# Nonopioid Pharmacologic Treatments

## Nonopioid Pharmacologic Treatments

The following section describes a variety of nonopioid pharmacologic treatment options for pain management. The table below summarizes these medications.

### Table 1 | Summary of Multimodal Analgesic Agents

| Type | Example |
|---|---|
| Nonopioid analgesics | APAP, NSAIDs (Cox-1, 2, 3 inhibitors) |
| Amine reuptake inhibitors | Duloxetine, venlafaxine, amitriptyline, nortriptyline |
| Antipsychotics | Haloperidol, olanzapine |
| Gabapentinoids/antiepileptics | Gabapentin, pregabalin, carbamazepine, topiramate |
| Glucocorticoids | Dexamethasone, prednisone |
| Local anesthetics/sodium channel blockers | Lidocaine, bupivacaine |
| Muscle relaxants/antispasmodics | Cyclobenzaprine, tizanidine, methocarbamol, metaxalone, baclofen, dicyclomine |
| Other topicals | Capsaicin, diclofenac, lidocaine, menthol |

## APAP

- **Evidence:** APAP has been shown to significantly reduce pain compared to placebo without increased adverse events. The number needed to treat (NNT) to achieve pain relief is 4.[1] Combined treatment with APAP (1000 mg) and ibuprofen (400 mg) appears to be as effective as oral opioid combinations (eg, oxycodone or hydrocodone with APAP) for the treatment of acute extremity pain.[2]
- **Mechanism of Action:** While not completely understood, the drug's mechanism of action is theorized to be the activation of descending serotonergic pathways. APAP increases the pain threshold by inhibiting central prostaglandin synthesis (specifically, cyclooxygenase [COX-2]).

- **Dosing:** APAP is a readily available, inexpensive, effective option for most mild to moderate pain conditions. Doses of 400 to 1000 mg can be given every 4 to 8 hours, not to exceed 4000 mg/day in healthy patients.
- **Contraindications and Cautions:** Life-threatening cases of acute hepatic failure that lead to liver transplant or death have been linked to the use of APAP. In most cases of hepatic injury, APAP doses exceeded maximum daily limits and often involved the use of more than one APAP-containing product. Hepatotoxicity has been reported with doses of 4 g or more per day; therefore, a lower maximum dose of 3 g per day in adults with normal liver function is recommended, particularly if the duration of use exceeds 7 days.
- **Hepatic Dosing:** In patients with cirrhosis and stable liver function tests, a maximum total daily dose of 2 g is recommended.[3]
- **Monitoring:** Check liver function tests, especially if the patient has pre-existing liver disease.
- **Instructions:** Instruct the patient to avoid other over-the-counter products that contain APAP, and limit the total daily dose to less than 3000 mg.

## Amine Reuptake Inhibitors/Antidepressants

- **Evidence:** Although chronic pain and depression are often comorbid conditions, amine reuptake inhibitors are thought to produce an antihyperalgesic effect (independent of their mood-stabilizing ability) by suppressing the noradrenergic descending inhibitory system.[4] Antidepressants have been widely used off-label for the treatment of chronic pain. In particular, venlafaxine (an SNRI) and nortriptyline (a TCA) should be strongly considered for the first-line treatment of neuropathic pain.[5–10] Low-dose TCAs have an average NNT of 2.6 (range 2.0–5.0) for neuropathic pain.[11] In addition to pain relief, TCAs can offer added benefit to patients with depression or whose pain is interfering with sleep. Duloxetine (an SNRI) should also be considered, as it is noninferior to pregabalin for the treatment of pain in patients with diabetic peripheral neuropathy.[12–14] Duloxetine and TCAs may reduce abdominal pain and increase quality of life in patients with irritable bowel syndrome.[15] Duloxetine should be considered as an adjunct therapy for patients with chronic neuropathic or abdominal pain who are receiving other first-line treatments. Duloxetine has also been shown to be effective for fibromyalgia and chronic musculoskeletal pain and is a first-line agent in patients with chronic pain and depression.[16] A systematic review found that there were no differences between venlafaxine and either gabapentin, pregabalin or duloxetine on average pain scores or the likelihood of achieving significant pain relief.[17]
- **Mechanism of Action:** Influence on affective components of pain. TCAs and SNRIs increase the concentration of norepinephrine in the spinal cord, a process that inhibits neuropathic pain through a2-adrenergic receptors.
- **Options:** SNRIs (eg, duloxetine, venlafaxine) and tricyclic antidepressants (TCAs) (eg, amitriptyline, nortriptyline)
- **Dosing:** Dosing should be based on effect and tolerability. Duloxetine: Start at 30 mg daily, then increase to 60 mg after 1 week. Venlafaxine: Start at 75 mg daily, then increase by 75 mg every 4 days to 150-225 mg daily. Amitriptyline: Start with 10 mg at bedtime; may titrate up to 50 mg at bedtime. Nortriptyline: 12.5 mg once daily at bedtime; may increase as tolerated up to 35 mg/day. Best used for chronic pain. Do not stop abruptly. May take 1 week or longer to take effect.
- **Contraindications and cautions:** SNRIs and TCAs may increase the risk of suicide in patients aged 18 to 25 years. Avoid TCAs in the elderly (Beers criteria) due to anticholinergic effects.

- **Monitoring:** Patients taking SNRIs should be monitored for serotonin syndrome. Monitor the QT interval (at baseline and periodically) of patients taking TCAs.
- **Instructions:** Close follow up is essential to ensure appropriate titration to target doses. (These medications require time to reach an effective dose, and an adequate duration should be trialed before concluding treatment failure.) Provider oversight is also important to monitor for adverse effects and initiate the safe discontinuation of therapy if deemed necessary.

## Antipsychotics

- *Haloperidol*
  - **Evidence:** Haloperidol is a first-generation antipsychotic agent that is often used for psychiatric emergencies. It has analgesic and antiemetic properties and shown to be an effective treatment for cyclic vomiting and cannabis hyperemesis syndrome, both of which can be very difficult to treat with physicians resorting unfortunately to opioids for pain control.[18,19] Haloperidol should be considered a first-line treatment option as part of an opioid-sparing pathway for these conditions. At doses of 2 to 5 mg, the drug is effective for the management of abdominal pain and migraine-associated headaches.[20,21] It has been shown to reduce pain intensity and nausea scores in patients with suspected gastroparesis.[22]
  - **Mechanism of Action:** Nonselective blockade of postsynaptic dopaminergic D2 receptors. Its mechanism of action for pain reduction is not completely understood. Antiemetic effects are thought to be due to blockade of these receptors in the chemoreceptor trigger zone. It also has weak anticholinergic effects.
  - **Dosing:** 2-5 mg IM/PO.
  - **Options:** It can be administered intramuscularly or orally.
  - **Contraindications and Cautions:** Use caution if treating patients with QT-prolonging conditions, concomitant QT-prolonging drugs and underlying cardiac abnormalities. Use with caution in older adults.
  - **Monitoring:** Obtain baseline ECG and repeat periodically during therapy.

- *Olanzapine*
  - **Evidence:** While a first-line treatment for schizophrenia, there is growing evidence to support the antiemetic properties of olanzapine, particularly in chemotherapy patients.[23] The analgesic properties of olanzapine have also been noted in randomized control trials focused on the treatment of migraine headaches and fibromyalgia.[24,25] Based on expert opinion and clinical experience, olanzapine is recommended for the management of cyclic vomiting syndromes (particularly cannabis hyperemesis), for which it appears to offer both analgesic and antiemetic benefits.[26] The drug may be an effective agent for the treatment of other painful conditions, including headaches and fibromyalgia.
  - **Mechanism of Action:** Olanzapine is a second-generation atypical antipsychotic with high affinity for serotonin and dopamine receptors, as well as antagonist activity at muscarinic receptors. However, its exact mechanism of action for antipsychotic effects is still relatively unknown.[27]
  - **Dosing:** Recommended initial dose is 2.5-5 mg IM/SL/PO. The 5 mg ODT product may be recommended every 6-8 hours as needed for nausea, vomiting, or abdominal pain.
  - **Options:** Olanzapine can be given intramuscularly, orally, and as an oral disintegrating tablet.

- **Contraindications and Cautions:** Somnolence, orthostatic hypotension and cardiac conduction abnormalities have been reported with olanzapine use. Caution should be exercised when prescribing high doses and in patient populations known to metabolize olanzapine more slowly (eg, nonsmokers, women, elderly).

## Capsaicin

- **Evidence:** Capsaicin is the derived active ingredient in chili peppers and is a natural analgesic produced in topical applications including creams, ointments and patches. It acts on nociceptive pain fibers by desensitization, thus inhibiting pain transmission.[28] Topical capsaicin has shown benefit in multiple applications including rheumatoid arthritis, osteoarthritis, and post-herpetic neuralgia.[29] While evidence is of lesser quality, research and experience is mounting for capsaicin being an effective treatment of pain associated with cannabis hyperemesis syndrome. Before higher quality evidence is available (which may be difficult due to the inherent nature of blinding a skin irritant), capsaicin is suggested to be used as an adjunct for cannabis hyperemesis syndrome. This can be particularly helpful as a possible abortive therapy for use at home, as it is also available over the counter and easy to apply. It is used by applying a thin layer over the abdomen. Additionally, capsaicin is considered category B for pregnancy risk factor with no observed adverse events in animal reproduction studies, which may allow more widespread administration as well as prior to pregnancy test results.[30–32]
- **Mechanism of Action:** Causes warmth/burning sensation by binding nerve membrane receptors. Initially stimulates then desensitizes and degenerates cutaneous nociceptive neurons; substance P depletion may also reduce pain impulse transmission to the CNS.
- **Dosing:** Creams and ointments are likely to be the most convenient, and come in forms including from 0.025% to 0.1%. Capsaicin 0.1% cream apply a thin layer to affected area four times daily as needed for pain.
- **Contraindications and Cautions:** May cause burning, redness or pain at the site of application. It has a very good safety profile, particularly when compared to other agents used for these common conditions.
- **Duration of Use:** Burning should reduce with repeated administration. May take 1-4 weeks for maximal pain relief.

## Dexamethasone

- **Evidence:** Glucocorticoids, and predominantly dexamethasone, have been shown to be efficacious in the treatment of acute migraine headache, dental pain, and sore throat, and may be an effective adjunct to other anti-inflammatories. Added to a typical headache regimen, dexamethasone has shown to have a reduction in headache recurrence at 24 and 72 hours in one metaanaylsis.[33] When given for postoperative dental pain, a single dose of dexamethasone has been shown to reduce pain up to seven days postoperatively.[34] When combined with gabapentin, increased dexamethasone led to improved analgesia after knee arthroplasty, suggesting a possible role in post-procedural pain control.[35]
- **Mechanism of Action:** Glucocorticoids (eg dexamethasone and methylprednisolone) have many actions including analgesic, antiemetic, antipyretic and anti-inflammatory effects. Although not completely clear, analgesic effects of dexamethasone are thought to result from the inhibition of phospholipase, leading to a decrease in cyclooxygenase and lipoxygenase production.
- **Dosing:** Dexamethasone 8-10 mg IM/PO as a single dose. Repeat dosing is rarely required.

- **Contraindications and Cautions:** Long term or repetitive use may increase risk of adverse events. Caution in patients at risk for gastric irritation. May lead to transient rise in blood glucose and require more frequent monitoring in diabetics. Repetitive or long term use may increase risk of adrenal suppression, poor wound healing, immunosuppression, myopathy, and psychiatric disturbances.

## Dicyclomine

- **Evidence:** It is effective for treating abdominal pain, particularly caused by cramping, and has been shown to be beneficial in irritable bowel syndrome.[36–39]
- **Mechanism of action:** Antispasmodic and anticholinergic effects that alleviate smooth muscle spasm of the GI tract.
- **Dosing:** Dicyclomine 10-20 mg IM/PO every 6 hours as needed for abdominal cramping.
- **Options:** Dicyclomine can be administered either orally or intramuscularly. It should NOT be administered intravenously due to risk of thrombosis and thrombophlebitis.
- **Contraindications and Cautions:** Dicyclomine can be an effective pain reliever in pregnant patients as a category B drug. Avoid use in elderly patients due to anticholinergic effects (Beers criteria) or patients at increased risk for delirium.[40] May worsen urinary retention or ileus.

## Gabapentinoids/Antiepileptics

- **Evidence:** 4 out of 10 patients with neuropathy will achieve 50% pain relief with gabapentin.[41] Pregabalin has better oral bioavailability and faster onset of action (1 hour vs 3 hours with gabapentin), although it is more costly. Pregabalin alone or combined with ibuprofen has shown efficacy with post-operative pain after third molar extraction.[42,43] Other antiepileptics (such as carbamazepine, oxcarbazepine, lamotrigine and topiramate) may have potential success at treating chronic neuropathic pain.[44]
- **Mechanism of Action:** Inhibits alpha 2-delta subunit of voltage-gated calcium channels, believe to decrease conduction of neuropathic pain sensation.
- **Dosing:** Gabapentin 300-600 mg or pregabalin 75-150 mg. Initiate with low doses and titrate to effective dose based on tolerability. Gabapentin: start at 100-300 mg PO 3x/day, then increase by 100-300 mg/day every 1-7 days as tolerated up to 1200 mg 3x/day. Pregabalin: start at 75 mg PO 2x/day, then increase by 150 mg/day every 3-7 days as tolerated up to 300 mg PO 2x/day.
- **Renal Dosing:** Adjust dose for renal impairment.
- **Contraindications and Cautions:** Avoid use in older adults with a history of falls as it may cause syncope, impaired psychomotor function or ataxia. Caution is advised in patients taking concomitant opioids or CNS depressants, with underlying respiratory diseases such as COPD and in elderly patients due to risk of increased respiratory depression. Avoid abrupt discontinuation.
- **Monitoring:** Consider checking serum creatinine.
- **Other Considerations:** Gabapentinoids have potential for misuse and abuse. Pregabalin is a Schedule V controlled substance. Although it has the lowest potential for abuse relative to other controlled substances, it does require the prescribing provider to have an active DEA number.

## Local Anesthetics

- *Local Injection:*
  - **Evidence:** Administration of LAs via subcutaneous infiltration is ideal for minor, localized injuries or procedures such as open wound repair, abscess drainage and foreign body removal. Local anesthetics also appear to have potential analgesic properties for both the treatment of acute and chronic pain when used as an intra-articular injection.

Evidence suggests intra-articular lidocaine provides a similar success rate for shoulder reductions compared to intravenous sedation.[45] However, intra-articular lidocaine also appears to have fewer complications, shorter length of stay, and lower cost compared to intravenous sedation.[46,47] Even for the treatment of chronic knee pain, such as that from osteoarthritis, local anesthetics may have potential for pain relief. A double-blind, RCT demonstrated reduction in pain at 3 months after three weekly intra-articular injections of 0.5% lidocaine in those with osteoarthritis.[48]

- **Mechanism of Action:** Blocks conduction of nerve impulses through inhibition of sodium channels.
- **Options:** Bupivacaine is a common alternative LAs that may be preferred due to their higher potency and longer duration of action.
- **Cautions:** Side effects of these drugs are minimal when used sparingly or in low doses.

- *Topical*
  - **Evidence:** Lidocaine is effective in a transdermal (4% or 5%) patch that may be used on intact skin for controlling neuropathic pain, post-herpetic pain, musculoskeletal injuries, and low back pain.[49,50] Other formulations of lidocaine, including ointment and creams, may be effective during painful procedures such as wound debridement, or for minor acute injuries involving broken skin, such as road rash, abrasions, and burns.[51] Lidocaine 5% patches, topicals or spray can be used for the treatment of a range of painful conditions that are resistant to other treatment modalities.[52,53] There is some information that over-the-counter lidocaine patches with menthol may actually have superior efficacy for pain management than prescription versions that do not have menthol. These have also been shown useful in decreasing pain to a tolerable level for participation in active therapy.[54]
  - **Mechanism of Action:** Blocks conduction of nerve impulses through inhibition of sodium channels.
  - **Dosing:** Lidocaine 4% or 5% transdermal patch to affected area of intact skin every 24 hours.[55] Up to 3 patches may be applied in a single application. Lidocaine 5% cream apply to affected area up to six times daily. Lidocaine 5% ointment apply up to 5 g to affected area four times daily.
  - **Contraindications and Cautions:** Transdermal patches are only recommended to use on intact skin. Creams or ointments may be used on minor injuries of broken skin.
  - **Discharge:** If 5% prescription concentration is cost prohibitive, can prescribe lidocaine 4% which is over-the-counter.

## Menthol Topical

- **Evidence:** Methyl salicylate and menthol provide significant pain relief of muscle strain compared to placebo.[56] In a small study, menthol was more effective than ice.[57]
- **Mechanism of Action:** Stimulates receptors producing cold sensation
- **Contraindications and Cautions:** Recommend use only on intact skin.

## Muscle Relaxants/Antispasmodics

- **Evidence:** Cyclobenzaprine reduces low back pain with an NNT of 3.[58] It can also reduce pain scores in patients with renal colic who are receiving NSAIDs, though the difference was not statistically significant.[59] There are many other types of muscle relaxants and antispasmodic options available, including but not limited to baclofen, tizanidine, dantrolene, carisoprodol,

orphenadrine, metaxalone and methocarbamol, for which there is mixed supporting literature. For most individuals, a short-acting muscle relaxant such as tizanidine or methocarbamol may be more appropriate as a first-line therapy, especially if taken only at night. Carisoprodol, chlorzoxazone and chlormezanone are not indicated due to concerning safety profiles.[52]

+ **Mechanism of Action:** Cyclobenzaprine: acts in the brainstem and reduces tonic somatic motor activity; structurally similar to TCAs. Tizanidine: alpha-adrenergic agonist. Methocarbamol and metaxalone: depresses CNS activity resulting in musculoskeletal relaxation. Baclofen: inhibits transmission of spinal synaptic reflexes.
+ **Antispasmodic Options:** cyclobenzaprine, tizanidine, methocarbamol, metaxalone. If spasticity (not spasm), consider baclofen.
+ **Dosing:** Start at a low dose and increase to effect while monitoring sedation. Cyclobenzaprine 5-10 mg PO 1-3x/day. Tizanidine 2-4 mg PO 1-2x/day. Methocarbamol 800 mg PO 3-4x/day. Baclofen 5-10 mg PO 3x/day.
+ **Contraindications and Cautions:** Avoid use in elderly patients (Beer's criteria) or patients at increased risk for delirium. [40] All antispasmodics may cause sedation, but anecdotally less sedation is seen with methocarbamol. For tizanidine, may cause bradycardia, hypotension.
+ **Duration of Use:** Use for shortest possible duration due to sedative side effects. Do not abruptly discontinue baclofen.

## Non-Steroidal Anti-Inflammatory Agents

+ **Evidence:** When combined with APAP, NSAIDs can reduce acute pain by 50% in 7 out of 10 patients.[60] Adding an NSAID to a pain regimen containing an opioid may have an opioid-sparing effect of 20% to 35%.[61] For renal colic, both opioids and NSAIDs lead to a clinically relevant reduction in pain scores; however, opioids are associated with higher rates of adverse reactions, particularly vomiting.[62] While a 2015 Cochrane review found that there was insufficient evidence to either support or refute the use of oral NSAIDs to treat neuropathic pain conditions, the American College of Occupational and Environmental Medicine Practice Guidelines recommend the use of generic ibuprofen, naproxen or other older generation NSAIDs as second-line agents for neuropathic pain, after tricyclic or SNRI antidepressants. They note that side effect profiles may make NSAIDs preferable to antidepressants for some patients.
+ **Mechanism of Action:** Inhibits proinflammatory prostaglandin production via the inhibition of COX-1 and COX-2 enzymes.
+ **Options:** Ibuprofen, naproxen, ketorolac, diclofenac, indomethacin, and selective COX-2 inhibitors (eg, meloxicam, celecoxib)
+ **Different Side Effect Profiles:** In general, COX-2 selective NSAIDs have a lower risk of GI side effects but a higher risk of cardiac side effects. Conversely, nonselective NSAIDs pose a lower risk of cardiac side effects but a higher risk of GI side effects.
+ **Contraindications and Cautions:** NSAIDs increase the risk of myocardial infarction and stroke. Contraindicated in the setting recent coronary artery bypass graft surgery or myocardial infarction. Can also cause increased risk for GI adverse events including bleeding, ulceration and perforation of the stomach or intestines. Risk is especially increased in elderly (Beer's criteria) and in patients with prior peptic ulcer disease or GI bleeding[40]. Caution should also be used in patients on concomitant anticoagulants or antiplatelet agents. Avoid use in patients with chronic kidney disease, cirrhosis or heart failure. Risk of renal injury is higher in patients who are elderly, dehydrated or with other comorbidities including heart failure, diabetes and cirrhosis.
+ **Special Considerations:** Special caution should be used in patients with renal dysfunction, heart failure, and concern for bleeding.[63] For these subpopulations, consider using topical choices

such as diclofenac gel or patch. Topical options have significantly lower systemic absorption and lower rates of adverse drug events.

- **Monitoring:** Check serum creatinine and discuss history of GI ulceration prior to initiation.
- **Recommended Duration of Use:** Use the lowest effective dose for the shortest possible duration.

### Table 2 | Risk of Gastric Ulcer Bleeding with NSAIDs[64]

| Individual NSAID | | Adjusted Conditional RR (95% CI) |
|---|---|---|
| Low ↕ High | **Celecoxib** | 1.0 (0.4-2.1) |
| | **Ibuprofen** | 4.1 (3.1-5.3) |
| | **Naproxen** | 7.3 (4.7-11.4) |
| | **Indomethacin** | 9.0 (3.9-20.7) |
| | **Ketorolac** | 14.4 (5.2-39.9) |

### Table 3 | GI Risk Factor Assessment and NSAID Therapy

| GI Risk Factor Assessment | Treatment |
|---|---|
| **High Risk**<br>+ **History of previously complicated ulcer, especially recent**<br>+ ***OR* more than 2 risk factors:**<br>  + **Age >65 years**<br>  + **High-dose NSAID therapy**<br>  + **Previous history of uncomplicated ulcer**<br>  + **Concurrent use of aspirin, corticosteroids, or anticoagulants** | Alternative therapy or COX-2 inhibitor + PPI |
| **Moderate Risk (1-2 risk factors)** | NSAID + PPI |
| **Low Risk (No risk factors)** | NSAID alone |

**Source: American College of Gastroenterology Guidelines, 2009[65]**

## Topical NSAIDs

- **Evidence:** To achieve a 50% reduction in musculoskeletal pain, NNT was 3.7 for topical diclofenac topic solutions which is about the same for oral NSAIDs[66] Only about 5% of topical NSAIDs are systemically absorbed compared to oral NSAIDs but studies show there is local absorption into tissues and synovium. Topical formulations are most effective when the pain is located in a superficial tissue[52] Topical NSAIDs may be more appropriate for some patients with chronic pain, as there is some evidence that topical NSAIDs are associated with fewer systemic adverse events than oral NSAIDs. These can also be used selectively as a later-line agent for the treatment of neuropathic pain. One randomized controlled trial determined effective

penetration of topical diclofenac sodium 4% spray gel into the synovial tissue and synovial fluid of the knee.[67] This and several other studies concluded that topical diclofenac presents an effective alternative to systemic NSAID therapy for the treatment of osteoarthritis, soft tissue injury including sprains and strains, and tendon pain particularly in the hands and feet.[67–77] Diclofenac is particularly useful in patients at risk for GI side effects or with hepatic or renal disease who cannot tolerate systemic treatment. Topical ketoprofen offers similar benefits but has been studied infrequently.[69] Topical NSAIDs may be considered in patients who have relative contraindications to oral NSAIDs.

+ **Mechanism of Action:** Inhibits proinflammatory prostaglandin production via inhibition of COX-1 and COX-2 enzymes.
+ **Options:** diclofenac gel, patch and solution.
+ **Contraindications:** Similar side effect profile to oral NSAIDs however a meta-analysis showed systemic adverse events were uncommon and did not differ from placebo[78]
+ **Other Considerations:** More expensive than oral NSAIDs.

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