



Non-Opioid Medications for Pain Relief

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Introduction

Acute and chronic musculoskeletal pain conditions are among the most common reasons prompting patients to seek medical care. Effective management of acute and chronic non-cancer pain and post-operative pain can improve quality of life and outcomes of care.

Opioid pain relievers are often prescribed to relieve musculoskeletal pain, and over the past few decades, there has been a significant increase in prescriptions of opioid pain relievers. While there is good evidence of efficacy of opioids to treat acute pain, there is a lack of consensus on the role of opioids to treat chronic non-cancer pain due to:

- limited long term efficacy (e.g. significant pain relief achieved in perhaps only 25% of patients)
- potentially significant side effects including constipation, nausea, sedation, increased falls, mood changes, and depressed breathing
- long term risks including misuse, abuse, addiction, overdose, and death

Unfortunately, the over prescribing of opioids has resulted in an epidemic of opioid use disorders and complications including overdose and death. In an effort to stem the tide of opioid deaths, guidelines have been developed to promote more judicious and safer opioid prescribing, including the release of Centers for Disease Control and Prevention Guideline for Prescribing Opioids for Chronic Pain.¹

Physicians and patients should also promote effective, non-opioid treatment options for pain including:

- non-opioid medications
- physical therapy and exercise
- complementary and alternative medicine
- interventional treatments including injections
- other considerations²

To improve symptoms and enhance recovery of function, treatment of chronic pain should include patient education regarding goals, risks, and benefits of different options. Medications should not be used as an isolated treatment, but rather prescribed in conjunction with other care options. The type of pain is a factor in the initial selection of medication to prescribe. For example:

- Acute pain due to an injury, such as a sprain (i.e. nociceptive pain) may respond well to medications such as non-steroidal anti-inflammatory drugs (NSAIDs). However, other medications (described below) may be required to treat chronic pain resulting from dysfunction of the nervous system, such as complex regional pain syndrome (i.e. neuropathic pain).
- Individual patients may respond differently to medications, and thus care may involve trials of different medications, or use of a combination of medications.
- Some patients may not be able to use certain medications due to side effects or personal medical conditions (e.g. liver, kidney, lung, neurologic disorders) that preclude use.

Thus patients and their physicians need to work together to determine the most effective treatment regimen with the fewest risks and side effects. In general, a clinically significant improvement should target at least 30% improvement of pain documented by accepted pain inventories, and the goal of therapy should also include quantified improvement in function.³

¹ <https://www.cdc.gov/drugoverdose/prescribing/guideline.html>

² <https://www.cdc.gov/drugoverdose/prescribing/patients.html>

³ <https://www.ncbi.nlm.nih.gov/pubmed/18165753>

The focus of this newsletter is to briefly discuss non-opioid medications used to treat pain.

Non-Opioid Medication Options

Non-steroidal anti-inflammatory drugs (NSAIDs)

NSAIDs are a class of medication that inhibits the enzyme cyclooxygenase, a chemical involved in the inflammatory process. NSAIDs include over the counter (OTC) (e.g. ibuprofen, naproxen) and prescription drugs, and are available in oral and topical formulations. Some NSAIDs act selectively on the enzyme pathway (cox-2 inhibitors, such as celecoxib), and were designed in an effort to cause fewer gastrointestinal side effects.

NSAIDs are commonly used as first line agents to treat mild to moderately painful conditions, such as acute sprains, strains, or contusions, in addition to having efficacy for arthritic disorders. NSAIDs appear to be more effective than acetaminophen to treat acute low back pain. For patients who are treated with opioid pain relievers, NSAIDs may help achieve pain control at lower opioid doses. NSAIDs may be used to treat chronic pain conditions, such as osteoarthritis or low back pain, though there are fewer studies in these settings. There is no evidence that any one NSAID is more effective than another, or that cox-2 inhibitors are better for pain than non-selective NSAIDs. However, at times some patients may find more benefit or fewer side effects from certain NSAIDs and thus, if one NSAID is not effective or tolerated, it is reasonable to consider a trial of a different NSAID. Occasionally, patients who have focal pain (e.g. acute knee pain) and cannot tolerate oral NSAIDs may be candidates for time limited treatment with certain non-compound topical NSAIDs when supported by guidelines and formulary.

As with all medications, NSAIDs have side effects and may be contraindicated in some patients.

- Non-selective NSAIDs interfere with the function of platelets and may therefore cause bleeding. Thus patients with bleeding disorders, high risk for bleeding (e.g. history of bleeding ulcer), or individuals taking anti-coagulants (“blood thinners”) may not be candidates for use of NSAIDs.
- Gastrointestinal (GI) side effects including reflux, dyspepsia, and ulcer disease may occur, thus limiting use.
- Patients at high risk due to ulcer disease or chronic steroid use may not be able to use NSAIDs.
- At times, use of proton pump inhibitors (PPIs), such as omeprazole (Prilosec), etc. may help patients tolerate NSAIDs or decrease the risk of GI side effects. However, longer term use of PPIs have risk of side effects as well, and benefits must be balanced by consideration of risks of PPI use.
- All NSAIDs are associated with increased risk of cardiovascular events, though a few studies suggest a decreased risk with naproxen vs. other NSAIDs.
- Use may be contraindicated or limited for patients with heart disease or history of thrombophlebitis.
- NSAIDs may cause kidney injury and fluid retention, thus raising caution for patients with renal disease, hypertension or heart disease.
- Some patients may be allergic to NSAIDs and at times, asthmatic patients may experience problems using NSAIDs.

In general, NSAIDs are effective, reasonably well tolerated by many patients, and remain first line agents for pain unless contraindicated or side effects preclude use.

Acetaminophen

Acetaminophen is an OTC medication that, while it does not have anti-inflammatory properties, may be used to treat mild to moderate pain in patients with acute pain conditions who are unable to take (i.e. bleeding disorders or anticoagulant use, GI problems, heart or kidney disease, etc.) or cannot tolerate NSAIDs. Acetaminophen appears to be less effective than NSAIDs for low back pain and osteoarthritis. Like NSAIDs, acetaminophen may help achieve pain control at lower opioid doses when combined with opioid pain relievers.

Side effects include:

- liver toxicity
- a small increased risk of hypertension and kidney disease
- occasional allergic reactions

Considerations to decrease the risk of liver toxicity from acetaminophen use include avoiding daily doses over 3000 to 4000 mg per day (approximately ten to twelve 325 mg tablets or six to eight 500 mg extra strength tablets). Patients at risk for liver toxicity (e.g. mildly abnormal liver function studies, consumption of three or more alcoholic drinks per day) should not exceed a daily dose of 2000 mg per day. Patients with more significant liver disease should avoid use of acetaminophen. Overall, acetaminophen is reasonably well tolerated by many patients, and remains an option unless contraindicated or side effects preclude use for treating pain in patients who are unable to use NSAIDs.

Muscle Relaxants

Muscle relaxants include a wide range of agents prescribed theoretically to reduce spasm, though their precise mechanism of action is uncertain and may be due, at least in part, to their sedative properties. Recent studies have suggested that muscle relaxants may not be as effective as NSAIDs to treat acute low back pain, and there may be a lack of benefit from the addition of muscle relaxants to NSAIDs in this setting. The efficacy of muscle relaxants to treat subacute to chronic low back pain is also unclear. However, some physicians prescribe muscle relaxants for short term (e.g. up to two weeks) treatment of low back or neck back pain that persists despite an initial trial of NSAIDs or acetaminophen, or for acute exacerbation in patients with chronic low back or neck pain. Efficacy tends to diminish over time.

Characteristics of the use of muscle relaxants may include:

- Patients may experience sedation, dizziness, or lightheadedness, and thus are preferably used at night for symptom control.
- Patients who operate motor vehicles or hazardous equipment, work at heights, or perform similar tasks that require alertness should avoid taking muscle relaxants during the day, and may need to consider limiting use if night time prescription results in persistent morning sedation.
- May cause other side effects including dry mouth or urinary retention.
- Long term use of some muscle relaxants can affect liver function.

The use of carisoprodol (Soma) or benzodiazepines to treat musculoskeletal disorders are not supported by the Official Disability Guidelines (ODG) or American College of Occupational and Environmental Medicine (ACOEM) treatment guidelines due to side effects and the rapid development of tolerance and risks of dependence and misuse. Weaning may be required in some patients when discontinuing select muscle relaxants that have been prescribed at higher doses for longer periods of time.

Antidepressants

Antidepressants include a variety of medications from a number of different classes of pharmaceuticals. The use of antidepressants to treat acute pain is generally not supported by ODG and ACOEM guidelines. However, there is evidence to support the treatment of chronic neuropathic pain (e.g. disc herniation with chronic radicular or post-operative pain, chronic pain due to complex regional pain syndrome, etc.), and perhaps chronic non-neuropathic pain as well (e.g. chronic non-specific neck or low back pain). The mechanism of action varies with the type of medication, but is believed to result in part from alteration of chemicals involved with transmission and modulation of pain signals in the nervous system. In addition, there are a number of patients with chronic pain who also have depression, and improvement of mood may potentially enhance patient coping and outcomes in some individuals. However, these medications may be beneficial to treat chronic pain in patients with and without depression. Of note, some antidepressants supported by ODG and ACOEM guidelines may not have U.S. Food and Drug Administration (FDA) indications for treatment of chronic pain, and prescription in those settings are considered "off-label".

There are two primary classes of antidepressants that have some demonstrated efficacy to treat chronic pain: tricyclic antidepressants (TCAs) and serotonin norepinephrine reuptake inhibitors (SNRIs). Another class called selective serotonin reuptake inhibitors (SSRIs) is used to treat depression; however, they do not appear to be effective in treating chronic neuropathic pain.

The decision regarding the class of antidepressant to try depends upon a number of factors including the patient's diagnosis, desired goals, and medical conditions that may limit use of specific drugs. Examples of side effects for TCAs (e.g. amitriptyline or imipramine, etc.) include:

- sedation (could be beneficial for a chronic pain patient who has sleep disturbance, but would preclude use for patients who experience persistent daytime drowsiness and are required to drive or require high levels of alertness at work)
- low blood pressure when standing (orthostatic hypotension)
- dry mouth
- constipation
- difficulty with urination
- arrhythmias (electrocardiogram may be indicated to monitor some patients).

Side effects at times can be decreased by lowering the dose, selecting a different TCA, or changing the time when it is taken (e.g. taking medication earlier at night to decrease morning sedation). Older patients or individuals with heart disease and arrhythmias, urinary dysfunction, or glaucoma may not be candidates for TCAs. In general, the dose of TCAs prescribed to treat chronic pain is lower than the dose used to treat depression. Patients need to understand that it may take several weeks to experience benefit and, with higher doses, weaning may be indicated when discontinuing use.

SNRIs (e.g. duloxetine, venlafaxine, bupropion, etc.) have been used to treat mood disorders, and duloxetine is approved by the FDA to treat painful diabetic neuropathy, fibromyalgia, and chronic musculoskeletal disorders. Side effects can include:

- nausea
- constipation
- dizziness
- insomnia
- mood changes
- dry mouth
- worsening of hypertension

Duloxetine may cause abnormal liver function. Patients with significant liver or kidney disease may not be able to use duloxetine.

When prescribed, patients often start with lower doses that are titrated up while monitoring benefits and side effects. As with TCAs, it may take several weeks to experience benefit and weaning may be required when discontinuing use.

In general, antidepressants are considered first line agents to treat chronic pain unless contraindicated or side effects preclude use.

Anticonvulsants (ACEs), also referred to as anti-epilepsy drugs (AEDs)

There are a number of medications used to treat convulsions that also have evidence of efficacy to treat some chronic neuropathic pain conditions, possibly due to their modulating effects on nerve transmission. Some including gabapentin, pregabalin, and carbamazepine have FDA approval for neuropathic pain including painful diabetic or posttherapeutic neuropathy and fibromyalgia (pregabalin). There is also ODG and ACOEM guideline support for use of these medications to treat conditions, such as complex regional pain syndrome, chronic radiculopathy, and spinal stenosis or post-operative neuropathic pain. However, these drugs are not indicated for acute pain or chronic non-neuropathic pain (e.g. chronic non-radicular neck or back pain, osteoarthritis).

Similar to antidepressants, the selection of the specific medication to try depends upon the patient's diagnosis, desired goals, medical conditions that may limit use of specific drugs, and side effects. Treatment is commonly initiated at lower doses and titrated to a higher dose depending upon the response and side effects. It may take several weeks to experience benefit and, with higher doses, weaning may be indicated when discontinuing use. Side effects from gabapentin and pregabalin include:

- sedation
- dizziness
- mood changes

Gabapentin has potential for abuse. Starting at lower doses, use at night and slow titration may help limit these side effects. As with other medications, these side effects may limit use for some patients. Some anticonvulsants (less commonly prescribed for chronic pain, such as carbamazepine, valproate, etc.) require monitoring of blood counts and liver function.

Topical Agents

The use of topical agents for pain has grown significantly in recent years, though the evidence for many agents is limited or lacking (especially with compound topical agents where many components lack efficacy or FDA approval for the manner in which they are used, and are costly). ODG and ACOEM guidelines generally limit support to select non-compound topical agents to treat specific localized conditions, primarily when oral agents are contraindicated or not tolerated. The following topical agents have some ODG and ACOEM guideline support:

- Topical NSAIDs including Voltaren (diclofenac) gel 1% or Flector (diclofenac) patch 1.3% for short term treatment of acute sprains or strains, osteoarthritis, or tendonitis of localized joints, such as the knee, elbow, or hand.
 - These agents are not supported for conditions with non-localized or widespread pain, joints that are not amenable to topical treatment (e.g. osteoarthritis of the hip, shoulder, back), or neuropathic pain.
 - Patients should not take oral NSAIDs while using topical NSAIDs or exceed dose limits (due to potential liver toxicity).
 - Topical NSAID combined with dimethyl sulfoxide (Pennsaid solution) is not supported by ODG guidelines due to increased side effects.
 - Patches may cause allergic reactions and should not be applied to non-intact skin.
- Topical lidocaine including Lidoderm 5% patches and lower cost OTC lidocaine 4% patches have ODG and ACOEM guideline support for treatment of localized neuropathic pain when other first line agents (TCAs, SNRIs, ACEs, such as gabapentin or pregabalin) are contraindicated or not effective.
 - These agents are not supported for non-localized or widespread pain, trigger points, myofascial pain, osteoarthritis, or non-specific neck or back pain.
 - Patches may cause allergic reactions and should not be applied to non-intact skin.
- Capsaicin cream is derived from chili peppers and may be used as an adjunct to treat localized pain from musculoskeletal disorders, such as back or neck pain or osteoarthritis.
 - This cream may have some efficacy for localized neuropathic pain, such as diabetic neuropathy.
 - Some patients are not able to tolerate side effects of topical burning, stinging, redness, etc.

There is a lack of evidence to support topical treatment using muscle relaxants, antidepressants, or anticonvulsants alone or compounded with other medications. Thus these agents are not recommended by ODG or ACOEM guidelines.

Conclusions

There are a number of options in the treatment of pain. Generally, non-medication treatment options including physical therapy and complementary or alternative treatments should be maximized, and medications used as adjunct treatments. OTC agents such as NSAIDs and acetaminophen are generally safe and effective when used as directed, though patients should be aware of potential contraindications and side effects. When considering prescribed medications for pain, patients and their providers should promote guideline-supported drugs for specific indications and consider potential contraindications. Patients should be followed to assess quantified benefit and monitored for side effects.

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7/21/2017