

Non-opioid Pharmacologic Therapy for the Treatment of Chronic Pain in Adults

The guidelines for the Management of Chronic Pain released by the CDC in 2016 recommends using nonpharmacologic and non-opioid therapies as the initial option for the treatment of chronic pain in adults. The following chart summarizes the uses and cautions that apply to many of the non-opioid analgesic medications. Doses are not definitive and must be individualized to the specific needs of the patient. Choice of agent should take into account other concurrent medical conditions and treatment modalities. The common use in chronic pain management represents both FDA approved indications and off-label uses. Some medications have multiple effects that can be used to treat the patient's pain as well as other comorbid conditions that are often found to co-exist with chronic pain (e.g. depression, anxiety, insomnia). Neuropathic pain encompasses multiple conditions, such as painful polyneuropathy (e.g. diabetic neuropathy), post-herpetic neuralgia, and central neuropathic pain.

Non-opioid Pharmacologic Therapy for Chronic Pain in Adults^{a, 2}

Drug	Common Use(s)	Suggested Dose(s)	Clinical Considerations
Analgesics			
Acetaminophen ¹⁵	Musculoskeletal pain	Up to 3,000-4000mg/day, divided doses dependent on formulation	<ul style="list-style-type: none"> • Not anti-inflammatory • Acetaminophen's recommended maximum daily dose (MDD) is 3000mg if patient is self-treating or 4000mg if their health care professional instructs them to do so. The MDD may be decreased for patients who consume alcohol (e.g. >3 alcoholic beverages per day) or have elevated liver enzymes
NSAID, COX-2 selective NSAID	Musculoskeletal pain	Indication specific	<ul style="list-style-type: none"> • Assess risk of nephrotoxicity, drug interactions, CV disease and GI toxicity prior to prescribing; administer with PPI or H2 blocker if GI intolerance or high risk; risk of cardiac adverse events (ibuprofen > naproxen); COX 2 agents maybe preferred agents for cardiac & renal safety; consider topical agents for individuals unable to use oral therapy
Anticonvulsants			
Carbamazepine ⁷⁻⁹	Trigeminal or glossopharyngeal neuralgia	Initial: 100mg/day, frequency is formulation dependent Titration: increase weekly by 100-200mg/day Effective: 200-400mg three times daily	<ul style="list-style-type: none"> • Common AEs: dizziness, drowsiness, ataxia, nausea, vomiting, xerostomia, weakness, blurred vision • Major AEs: aplastic anemia and agranulocytosis, serious dermatologic reactions (e.g. toxic epidermal necrolysis, Stevens-Johnson syndrome), test for HLA-B*1502 allele prior to initiating treatment in patients with Asian ancestry, including South Asian Indians, as they have an increased likelihood of carrying this allele • Consider monitoring blood levels, particularly after dosage adjustment. Watch for drug-drug interactions. Monitor liver function tests
Gabapentin ^{3-5,7,8,14}	Neuropathic pain, fibromyalgia	Initial: 100-300mg, 1-3x/day Titration: increase every 5 to 7 days by 300mg/day Effective: 900-3600mg/day, divided doses • DPN: 1800-3600mg/day, divided doses Duration of adequate trial: 3-8 weeks for titration plus 2 weeks at maximum dosage	<ul style="list-style-type: none"> • Common AEs: somnolence, dizziness, ataxia, fatigue, peripheral edema • Major AEs: Stevens-Johnson syndrome, suicidal thoughts and behavior, seizures after rapid discontinuation, thrombocytopenia • Requires renal dose adjustment • Slow initiation is recommended and should be done until minimal effective dose reached or intolerable side effects. When discontinuing, taper off gradually over at least 1 week
Pregabalin ^{3-5,7,8,10,14} *Brand only available (Lyrica®) *Controlled substance: C-V	Neuropathic pain, fibromyalgia	Initial: 25-75mg, 1-3x/day Titration: increase weekly by 50-150mg/day Effective: 300-600mg/day in divided doses • DPN: 300-600mg/day • Fibromyalgia: 150-450mg/day • SCI, post-herpetic neuralgia: 150-600mg/day Duration of adequate trial: 4 weeks	<ul style="list-style-type: none"> • Common AEs: somnolence, dizziness, peripheral edema, headache, ataxia, fatigue, xerostomia, weight gain • Major AEs: angioedema, hepatotoxicity, rhabdomyolysis, suicidal thoughts and behavior, seizures after rapid discontinuation, thrombocytopenia • Renal dose adjustment needed • Slow initiation is recommended, for example: 75mg at bedtime for a week, then increase by 50-75mg every 5 days as tolerated. When discontinuing, taper off gradually over at least 1 week • This product is more expensive compared to gabapentin.

Drug	Common Use(s)	Suggested Dose(s)	Clinical Considerations
Valproic acid ^{8,9}	Neuropathic pain	Initial: 500mg/day Effective: no specific dosing, doses as high as 1,200mg/day have been studied	<ul style="list-style-type: none"> • Common AEs: headache, drowsiness, dizziness, nausea, abdominal pain, tremor, weakness • Major AEs: peripheral edema, hepatotoxicity, pancreatitis, patients with mitochondrial disease (avoid use) • Considered to be 3rd drug for neuropathic pain. Watch for drug-drug interactions
Antidepressants			
Note: all antidepressants take approximately two weeks to exert their full analgesic effect at any particular dose ⁷			
TCAs ^{3-9,14,15} Amitriptyline	Neuropathic pain, fibromyalgia, depression, chronic pain, insomnia	Initial: 10-25mg/day Titration: increase weekly by 10mg/day Effective: 25-150mg/day • DPN: 25-100mg/day Duration of adequate trial: 6-8 weeks with at least 2 weeks at maximum tolerated dose	<ul style="list-style-type: none"> • Common AEs: xerostomia, somnolence, fatigue, headache, dizziness, insomnia, orthostatic hypotension, anorexia, nausea, urinary retention, constipation, blurred vision, accommodation, disturbance, mydriasis, weight gain • Major AEs: delirium, cardiac arrhythmias, conduction abnormalities, myocardial infarction, heart failure exacerbation, stroke, seizures, hepatotoxicity, bone marrow suppression, suicidal thoughts and behavior, shift to mania in bipolar disorder, neuroleptic malignant syndrome, serotonin syndrome, severe hyponatremia, fragility bone fractures • NOTE: TCAs, in general, should be avoided in patients >65 years of age due to their adverse effects. Nortriptyline and, to a lesser extent, desipramine are the TCAs of choice in the elderly. As secondary amines, they are associated with less anticholinergic, antihistaminic, and orthostatic hypotension. Cardiac toxicity is equal amongst the TCAs. Avoid use in dementia. Desipramine and nortriptyline doses should be limited to 25-50mg/day in the elderly.
Nortriptyline	Neuropathic pain, fibromyalgia, depression, chronic pain, myofascial pain, orofacial pain, insomnia		
Desipramine	Neuropathic pain, depression		
SNRIs ^{3-9, 14,15} Duloxetine	C-MSP (includes chronic low back pain or osteoarthritis of the knees), neuropathic pain, GAD, Major Depressive Disorder, fibromyalgia	Initial: 20-30mg/day Titration: may increase up to 60mg/day after one week Effective: 60-120mg/day Duration of adequate trial: 4 weeks	<ul style="list-style-type: none"> • Common AEs for both duloxetine and venlafaxine: nausea, somnolence, dizziness, constipation, dyspepsia, diarrhea, xerostomia, anorexia, headache, diaphoresis, insomnia, fatigue, decreased libido • Major AEs for both duloxetine and venlafaxine: Stevens-Johnson syndrome, hepatotoxicity, hypertensive crisis, gastrointestinal hemorrhage, delirium, myocardial infarction, cardiac arrhythmias, glaucoma, suicidal thoughts and behavior, shift to mania in patients with bipolar disorder, seizures, severe hyponatremia, fragility bone fractures, serotonin syndrome, neuroleptic malignant syndrome
Venlafaxine	Neuropathic pain, GAD, Major Depressive Disorder, panic disorder, social phobia, fibromyalgia	Initial: 37.5mg/day Titration: increase weekly by 37.5mg/day Effective: 150-225mg/day, single dose extended-release formulation • DPN: 75-225mg/day Duration of adequate trial: 4-6 weeks	<ul style="list-style-type: none"> • Duloxetine has more adrenergic activity and may potentially be "better" for chronic pain. Although it may be started at 60mg/day, there can be a higher incidence of side effects (e.g. nausea), especially in older adults (>65 years), so initiating at a lower dose is recommended. • Renal and hepatic dose adjustment is needed for both duloxetine and venlafaxine
Milnacipran *Brand only available (Savella®)	Fibromyalgia	Initial/titration: 12.5mg once on day 1, then 12.5mg twice daily on days 2-3, 25mg twice daily on days 4-7, then 50mg twice daily thereafter Effective: 100-200mg/day, divided doses	<ul style="list-style-type: none"> • Common AEs: Headache, insomnia, hot flash, nausea, constipation, palpitations, increased heart rate, hypertension, xerostomia, migraine • Major AEs: Suicidal thoughts and behavior • Potent inhibitor of norepinephrine and serotonin reuptake (3:1) with no significant activity for serotonergic receptors

Drug	Common Use(s)	Suggested Dose(s)	Clinical Considerations
Skeletal Muscle Relaxants			
Cyclobenzaprine ^{9,13,15}	Muscle spasm	Dose: 5mg 3x/day, may increase up to 10mg 3x/day if needed	<ul style="list-style-type: none"> • Common AEs: drowsiness, dizziness, xerostomia, headache, confusion • Use not recommended in moderate to severe hepatic impairment • NOTE: This is on the Beer's list as a high-risk medication in the elderly as it has moderate anticholinergic burden. Closely related to TCAs so should not be used in combination with other TCAs. Do not use longer than 2 to 3 weeks. Avoid long-term use in chronic pain.
Baclofen ^{9,13,15}	Spasticity	Dose: 5mg 3x/day, may increase up to 40-80 mg/day as needed	<ul style="list-style-type: none"> • Common AEs: hypotonia, drowsiness, urinary retention, urinary frequency, constipation, xerostomia, dizziness, paresthesia, hypertonia • Major AEs: seizure • NOTE: This is on the Beer's list as a high-risk medication in the elderly. Abrupt withdrawal of oral therapy has been associated with hallucinations and seizures; gradual dose reductions (over ~1 to 2 weeks) are recommended in the absence of severe adverse reactions.
Methocarbamol ^{9,13,15}	Muscle spasm	Dose: 1.5g 4 times/day for 2-3 days (up to 8 g/day may be given in severe conditions), then decrease to 4-4.5g/day in 3-6 divided doses	<ul style="list-style-type: none"> • AEs: bradycardia, flushing, hypotension, syncope, dizziness, nausea, urine discoloration (brown, black or green) • NOTE: This is on the Beer's list as a high-risk medication in the elderly. It is available in Canada as an OTC.
Tizanidine ^{9,15}	Spasticity	Dose: 2mg up to 3x daily, maximum 36mg daily	<ul style="list-style-type: none"> • Common AEs: hypotension, orthostatic hypotension (may be limiting factor), drowsiness, dizziness, xerostomia, weakness, bradycardia, constipation, anxiolytic • Gradually taper dose by 2-4mg daily when discontinuing therapy • Renal dose adjustment needed
Metaxalone ^{9,13}	Musculoskeletal conditions	Dose: 800mg 3 to 4 times daily	<ul style="list-style-type: none"> • AEs: dizziness, drowsiness, headache, irritability, nervousness, GI upset, hemolytic anemia, leukopenia • NOTE: This is on the Beer's list as a high risk medication in the elderly. Use with caution in liver disease.
Carisoprodol ^{9,13,15} *Controlled substance: C-IV	Musculoskeletal conditions	Dose: 250 to 350mg 3 times daily and at bedtime for a maximum recommended duration of 2 to 3 weeks	<ul style="list-style-type: none"> • Common AEs: drowsiness, dizziness, headache • NOTE: Avoid due to addictive potential as it is part of the "Holy Trinity" of addiction, which is a regimen that includes at least 1 opioid, a benzodiazepine, and carisoprodol. It is on the Beer's list as a high risk medication in the elderly. In patients with a history of long-term use or high doses, it should be tapered off slowly (e.g., over 14 days) to avoid withdrawal symptoms such as anxiety, insomnia, or irritability. Avoid use in chronic pain.
Topical Medications			
Lidocaine patch ^{5,7,9,12,14}	Neuropathic pain, localized pain	Dose: Apply patch to painful area. Patch may remain in place for a maximum of 12 hours in any 24-hour period Duration of adequate trial: 3 weeks	<ul style="list-style-type: none"> • Avoid use on traumatized mucosa, skin irritations • Up to 3 patches may be applied in a single application and may be cut to shape • The 5% prescription strength (\$6/patch) may require prior approval through the insurer whereas the OTC 4% patch is also effective and less expensive (\$3/patch)
Diclofenac gel/patch ^{9,15}	Localized musculoskeletal pain	Osteoarthritis: apply 4g to lower extremities 4x daily or 2g to upper extremities Acute pain (sprains, sprains, contusions): 1 patch applied twice daily to most painful area	<ul style="list-style-type: none"> • Avoid use on non-intact/damaged skin including dermatitis, eczema, burns or wounds • Diclofenac patch needs to be removed prior to MRI procedures

Drug	Common Use(s)	Suggested Dose(s)	Clinical Considerations
Capsaicin OTC cream, patch ^{5,9,15,16}	Localized muscle and joint pain, DPN	Muscle/joint pain: <i>Cream:</i> Apply thin film to affected areas 3-4 times daily. <i>Patch:</i> concentration dependent DPN: Cream (0.075%) applied 4 times/day	<ul style="list-style-type: none"> • Common AEs: Causes increased burning during initial use, which usually lessens within 72 hours with repeated use. Should not be used in acute herpes zoster due to risk of mucosal contact. • Avoid use on wounds, damaged/irritated skin. Do not cover with bandage or use with external heat source. Instruct patients to use a glove or plastic bag for application and wash their hands following use. • An adequate trial usually requires four applications daily, around the clock, for at least three to four weeks.
Isosorbide dinitrate spray ⁵	DPN	Dose: 30mg at bedtime applied to bottom of feet	
Methyl Salicylate, Menthol, Camphor ^{15,16}	Counterirritants	Apply no more often than 3 to 4 times daily for up to 7 days <ul style="list-style-type: none"> • Temporary relief of minor aches and sprains of muscles and joints • Simple backache, arthritis pain, strains, bruises, and sprains 	<ul style="list-style-type: none"> • Product availability: come in various forms (e.g. balms, creams, gels, and patches) under several different brands (e.g. BenGay®, Icy Hot®, Salonpas®) and either alone or in different combinations of counterirritants • Methyl salicylate: localized reactions (e.g. skin irritation or rash) and systemic reactions (e.g. salicylate toxicity) may occur

Abbreviations: NSAID - Nonsteroidal Anti-Inflammatory Drug. AE – adverse effect. SCI – spinal cord injury. C-MSP – chronic musculoskeletal pain. GAD – generalized anxiety disorder. TCA – tricyclic antidepressant. SNRI – serotonin-norepinephrine reuptake inhibitor. OTC – over-the-counter. DPN – diabetic peripheral neuropathy. CV – cardiovascular. GI – gastrointestinal. PPI – proton pump inhibitor. H₂ blocker – histamine H₂ antagonist.

a. This resource was initially adapted from the CPPM toolkit that has been in place since 2002. This resource was expanded in depth by Greater Rochester Independent Practice Association (GRIPA). This tool is now included in the CPPM Toolkit with permission of GRIPA.

The Community Principles of Pain Management (CPPM) is a professional resource approved by the Excellus Health Care Quality Monitoring Committee and the Monroe County Medical Society Quality Collaborative. It can be found on the Pain Guidelines web page: <https://compassionandsupport.org/pain-symptoms/pain-guidelines/> at <https://CompassionAndSupport.org/>

References: 1. The STOP measure: safe and transparent opioid prescribing to promote patient safety and reduced risk of opioid misuse. AHIP's safe, transparent opioid prescribing (STOP) initiative. America's Health Insurance Plans. February 2018. 2. Community principles of pain management (CPPM) . 3. Hooten MW. Chronic pain and mental health disorders: shared neural mechanisms, epidemiology, and treatment. Symposium on pain medicine. *Mayo Clin Proc.* 2016;(91)7:955-970. 4. Diabetic neuropathy: a position statement by the American Diabetes Association. *Diabetes Care.* 2017;40:136-154. 5. Snyder MT, Gibbs LM, and Lindsay TJ. Treating painful diabetic peripheral neuropathy: an update. *Am Fam Physician.* 2016;94(3):227-234. 6. Hutchison LC and Sleeper RB. Fundamentals of geriatric pharmacotherapy: an evidence-based approach. ASHP publications. 2015. 7. Moulin DE, Clark AJ, Gilron, et al. Pharmacological management of chronic neuropathic pain – consensus statement and guidelines from the Canadian Pain Society. *Pain Res Manage.* 2007; 12(1): 12-21. 8. Attal N, Cruccu G, Baron R, Haanpaa M, et al. EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. *European Journal of Neurology.* 2010, 17:1113-1123. 9. Lexicomp® [online database]. (accessed 2018 Feb 02). Hudson, Ohio. Wolters Kluwer Clinical Drug Information, Inc. 10. Drugs@FDA: FDA Approved Drug Products. Lyrica [monograph]. www.accessdata.fda.gov/drugsatfda_docs/label/2016/021446s032.022488s011bl.pdf (accessed 2018 Feb 22). 11. Bauman TJ and Stricklan S. Pain management. In: Dipiro JT, Talbert RL, Yee GC, eds. Pharmacotherapy a pathophysiologic approach. New York: McGraw-Hill; 2008:989-1003. 12. Castro E and Dent D. A comparison of transdermal over-the-counter lidocaine 3.6% and placebo for back pain and arthritis. *Pain Manag.* 2017. 13. American Geriatrics Society 2015 Beers Criteria Update Expert Panel. American Geriatrics Society 2015 updated beers criteria for potentially inappropriate medication use in older adults. *J Am Geriatr Soc.* 2015. 14. Dworkin RH, O'Connor AB, Backonja M et al. Pharmacologic management of neuropathic pain: evidence-based recommendations. *Pain.* 2007;132:237-251. 15. American Chronic Pain Association. ACPA resource guide to chronic pain management: an integrated guide to medical, interventional, behavioral, pharmacologic and rehabilitation therapy. 2017. 16. Wright E. Musculoskeletal injuries and disorders. In: Berardi SR, Ferreri SP, Hume AL, eds. Handbook of nonprescription drugs. An interactive approach to self-care. Washington, DC: APhA; 2009: 95-113.

This document is for informational purposes only. For more up to date information please refer to the medication's package insert available on the FDA website (www.accessdata.fda.gov/scripts/cder/drugsatfda/). Decisions regarding the pharmacological management of a patient's condition should be made based on the individual needs of the patient (i.e. frequency of dosing, duration of action needed).

Guidelines and principles are intended to be flexible. They serve as reference points or recommendations, not rigid criteria. Guidelines & principles should be followed in most cases, but there is an understanding that, depending on the patient, the setting, the circumstances, or other factors, care can and should be tailored to fit individual needs. Approved in June 2019; Next Scheduled Update in 2021