ALTERNATIVES IN PAIN MANAGEMENT

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Non-opiate pharmacotherapy options for the management of pain in older adults

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Abstract

Pain is highly prevalent, costly, and disabling in later life, especially when undertreated. In this article, we aim to describe the risks and benefits of non-opioid medication options for the management of pain in adults aged 65 years and older in order to provide additional options in a practitioner's tool box when designing a pain management regimen for an older adult. Non-opiate pharmacologic therapies, such as acetaminophen, nonsteroidal anti-inflammatory drugs, topicals, and antidepressants have an important role in pain management of older adults. When designing a pain regimen, taking an individualized approach that considers the patient's functional status, comorbidities, and treatment goals will maximize pain management.

Keywords: pain, geriatrics, alternatives, adjuvant, non-opioid, treatment, risks, benefits, elderly

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Introduction

Pain management in adults aged 65 years and older presents many challenges. Despite the fact that 25%–40% of community-dwelling older adults and up to 80% of those in long-term-care facilities experience pain, there are minimal clinical research or practice recommendations for pain management.[1] Additionally, as people age, their kidney and liver functions decline and gastrointestinal (GI) transit slows, increasing exposure to medications and risk of side effects. Therefore, many of the pain management guidelines for younger adults or children cannot be applied to the older adult population.

Pain in the older adult population is undertreated and underreported. Undertreated pain is associated with increased costs and many poor health outcomes, including functional impairment, falls, prolonged rehabilitation, caregiver distress, mood changes, and overall increased health care utilization.[1,2] Underreporting occurs because of cognitive impairment, patients' concerns about being a burden to their caregiver, a belief that pain comes with old age, and fear of medication side effects.[1,3,4] Those who have previously failed to obtain relief from medication may also believe pain is untreatable.

Cultural perceptions about the possibility of opiate addiction have resulted in a decrease in their use. This occurs at the expense of older adults who are truly experiencing pain. Patients and providers share a concern about the side effects and the potential for addiction with opiates.[4] Older adults are particularly susceptible to cognitive impairment, falls, constipation, and respiratory depression when taking opiates.[5] The recent change of hydrocodone/acetaminophen products to controlled substance class II has drastically decreased accessibility as a new prescription needs to be written and hand-delivered to the pharmacy each month. Tramadol, codeine/acetaminophen, and pentazocine/naloxone are now the only opiates that can be prescribed with refills. For the older

adult population, particular caution should be taken when prescribing tramadol because of the increased risk of serotonin syndrome when given with other medications that increase serotonin.

In this review, the risks and benefits of non-opioid therapies in older adults are explored to provide a variety of options for pain management in the older adult population.

Assessing Pain

Before treating an older adult's pain, adequate pain assessment must be completed. The gold standard continues to be self-assessment of pain. Self-report has been found to be reliable for patients with a Mini Mental State Examination (MMSE) score >10.[6,7] Studies have also documented that those with mild to moderate cognitive impairment, defined as a MMSE score of 18 or higher, are able to respond to unidimensional self-report scales as well as those with moderate to severe impairment, defined as a MMSE score of 12 to 17.[8] A wide variety of assessment tools are supported by varying evidence for their use in an older adult population; many of these have been validated for persons in multiple practice settings, including community-dwelling persons. Jones and colleagues[9] compared three tools, the Bieri Faces Pain Scale, Numeric Rating Scale, and Visual Descriptive Scale, to establish equivalency of mild, moderate, and severe pain for comparison in a nursing-home setting. To be eligible for the comparison, all patients had to be capable of verbally expressing pain. In this cohort, the Visual Descriptive Scale tool was preferred among patients. When the Bieri Faces Pain Scale was used, high-intensity pain was often underrated.[9] Although the Visual Descriptive Scale is generally preferred by older adults, it should be noted that it requires abstract thought and a higher command of language.[9,10] The Numeric Rating Scale uses a numeric scale ranging from 0 to ten, assuming that 10 is the worst pain imaginable to rate pain. This tool is generally preferred because of its psychometric properties, ease of use, and minimal linguistic demands. Those with cognitive impairment have difficulty with this scale, however, as they may not be able to recall previous pain episodes for comparison.[10,11]

Often, assessment of pain in a patient with cognitive impairment or the inability to respond requires assessment of nonverbal cues. Patients with cognitive impairment are more likely to express pain through increased vocalizations, grimacing, and verbal complaints.[12] Assessment of nonverbal signs of pain can be completed using the Checklist of Nonverbal Pain Indicators or Pain Assessment in Advanced Dementia scale.[12,13] Both scales assess a variety of factors, including vocalizations, facial expression, consolability, bracing, restlessness, and breathing patterns.[12,13]

Once a diagnosis of pain is made, assessment should be made continuously. Assessments should be done at least daily for inpatients and at every visit for outpatients. The goal of therapy is to reduce pain to a level where the patient is able to continue daily function. Complete elimination of pain is often an unattainable goal and may come at the risk of increased side effects from medication at the higher doses required for full resolution of pain.

Pain Types and Classification

By definition, pain is an unpleasant sensation that is both a sensory and emotional experience associated with an actual or potential tissue injury. Pain can be classified as acute, chronic (noncancerous), or cancer related. Distinguishing the type of pain is as important as the initial assessment of pain, as this will guide the choice of pharmacotherapy. Identification of the pain type, along with other comorbidities, will greatly affect the experience and expression of pain as well as the choice of treatment in older adults.

Acute pain is primarily nociceptive pain that is protective and physiologic and can be further divided into somatic and visceral pain. Somatic pain arises from skin, bone, joint, muscle, connective tissue, or malignancy and needs to be characterized as a throbbing sensation of pain that is localized. In contrast, visceral pain arises from organs and can be localized or referred.[14] Transmission of this pain occurs in the A-δ and C afferent nerve fibers, where A-δ fibers promote sharp and well-localized pain and the C fibers promote aching and poorly localized pain. Alterations in neurobiology of pain in older adults affect their threshold, tolerance and treatment.[15] Some researchers believe an increased pain threshold results in a prolonged time to reach discomfort before a patient becomes symptomatic. However, this population has a low pain tolerance and is unwilling to endure very strong pain.[15] Therefore, when acute pain syndromes are undertreated or unremitting, chronic pain may develop; thus, the goals of treatment should focus on reducing pain in the acute state.

Far too often, acute pain goes untreated, leading to pain that may last from months to years. Chronic pain may result from a sustained sensory abnormality occurring as a result of ongoing peripheral pathology, such as chronic inflammation. Chronic pain may also be autonomous and independent of the trigger that initiated the pain.[14] Chronic pain is broken down into nociceptive or neuropathic pain. Compared with acute pain, chronic pain is not connected with noxious stimuli or healing and may be

difficult to link with physical findings or imaging. Neuropathic pain can be caused by a lesion or disorder of the somatosensory system, resulting in pain circuits that rewire themselves and cause a mismatch between pain stimulation and inhibition.[16] Typically, the pain presents with an episodic or continuous sensation described as tingling, shocking, burning, or shooting. Some cases of neuropathic pain are a result of an exaggerated response to normal noxious stimuli, hyperalgesia, non-noxious stimuli, or allodynia.[16] This type of pain can continue long after the nerve-related injury has healed or when no injury has been found. See Table 1 for a list of types of neuropathic pain and respective origins.[17]

The literature also notes that the perception can contribute to intensity of pain. While not well understood, the theory is that it takes place in a higher cortical structure, where cognition and behaviors may modify pain perception. For example, meditation, distraction, and relaxation decrease pain, whereas stress, depression, and anxiety increase pain.[18] This is why the goals of chronic pain are quite different and lean toward increasing functionality rather than seeking remission of pain. See Table 2 for a comparison of acute and chronic pain.[19]

TABLE 1: Characteristics of acute and chronic pain

Characteristic	Acute Pain	Chronic Pain
Relief of pain	Highly desirable	Highly desirable
Dependence on medication	Uncommon	Common
Psychological component	Uncommon	Common
Organic cause	Common	Uncommon
Environmental/family issues	Small	Significant
Insomnia	Usual	Common
Depression	Uncommon	Common
Dependence on medication	Uncommon	Common
Treatment goal	Pain reduction	Functionality

Pharmacologic Options

Acetaminophen

Acetaminophen is well known for having an excellent safety profile, especially in frail older adults. The drug is widely available by prescription and over the counter in tablet, capsule, elixir, solution, suspension, chewable, orally dissolving tablet, suppository, parenteral, and extended-release formulations.[20] An emphasis on safety has placed acetaminophen as the first-line option in American Geriatrics Society and British Geriatrics Society guidelines, despite its generally being considered only moderately effective compared with short-term nonsteroidal anti-inflammatory drug (NSAID) treatment for such conditions as rheumatoid arthritis, lower back pain, and osteoarthritis.[2,21-23]

Where acetaminophen truly comes to the forefront is through its safety studies. Although other treatment options often have multiple side effects that are more pronounced in older adults, acetaminophen is considered safe at doses <4 g (4000 mg) per day.[24,25] Aminotransferases can become elevated in patients taking usual treatment doses of acetaminophen, but these elevations tend to be transient and cause no noticeable sequelae.[26] Unfortunately, many older adults are taking more acetaminophen than intended because of its presence in many over-the-counter and combination products. Some drug companies have voluntarily changed their monograph recommendations to 3 g/day, preferring the lower goal to reduce the risk of accidental overdose.[27] Excessive acetaminophen consumption, whether intentional or not, can lead to drug-induced hepatotoxicity and acute liver failure.

For every year beyond the age of 50, older adults lose a small percentage of their liver volume and blood flow. These changes may result in a reduced ability to compensate for hepatic insults and increased drug bioavailability due to reduced first-pass metabolism.[28] Older adults also have reduced phase I metabolism, which may offer some protection because of the reduced toxic metabolite production. However, older adults are also at higher risk for malnutrition, which can lead to decreased glutathione production and increased risk for acetaminophen-induced hepatotoxicity.[29] Although some studies state that doses <4 g/day are quite safe, others have suggested that doses >3 g/day of acetaminophen can lead to cardiovascular, GI, and renal side effects at a similar rate to NSAIDs due to inhibition of prostaglandin synthesis.[24,25,30]

As long as daily dose recommendations are not exceeded and the patient does not have impaired kidney and liver function, acetaminophen is generally tolerable and moderately effective.[21] Over-the-counter acetaminophen preparations are both inexpensive and convenient. American Geriatrics Society and British Geriatrics Society guidelines agree that acetaminophen doses <4 g/day from all sources should be tried before other options in most patients for pain management.[2,21] Counseling the patient on the many sources of acetaminophen is crucial for patient safety. If the patient's pain is not sufficiently relieved with acetaminophen monotherapy then adjuvant medications or alternative drug classes may be appropriate.[2,21,30]

Nonsteroidal Anti-Inflammatory Drugs

The NSAIDs have well-recognized adverse effects that often cause practitioners to overlook their effectiveness in

TABLE 2: Neuropathic pain guidelines

Condition	First-Line Agents	Second- or Third-Line Agents	Other Considerations
Painful polyneuropathy			
Diabetic and nondiabetic painful polyneuropathy	• TCA	• Tramadol	In diabetic and nondiabetic painful polyneuropathy:
	• Gabapentin/pregabalin	• Stronger opioids	• Gabapentin + TCA, opioid, or venlafaxine > gabapentin alone
	• Serotonin-norepinephrine reuptake inhibitor (venlafaxine, duloxetine)[a]		• Needs more study
Human immunodeficiency virus neuropathy	• Lamotrigine	Not applicable	
	• Smoked cannabis		
	• Capsaicin patches		
Postherpetic neuralgia	• TCA	• Capsaicin patches	Capsaicin patches show promise, but long-term effects are unclear
	• Gabapentin/pregabalin	• Opioids	
	• Topical lidocaine[b]		
Trigeminal neuralgia	• Carbamazepine	• Lamotrigine	• Efficacy in classical trigeminal neuralgia only
	• Oxcarbazepine	• Surgery	
Central neuropathic pain	• Amitriptyline	• Tramadol	Central neuropathic pain composed of:
	• Gabapentin/pregabalin	• Strong opioids	• Central post-stroke pain
		• Lamotrigine (central post-stroke pain, spinal cord injury)	• Spinal cord injury
		• Cannabinoids (multiple sclerosis)	• Multiple sclerosis
Radiculopathy (other NP)	Level A evidence[c]	Level B evidence[d]	No reliable positive results for treatment.
Cancer NP	• Gabapentin	• Amitriptyline	
		• Tramadol	
Multietiology NP	• Bupropion	• TCA	
	• Cannabinoids	• Methadone	
	• Levorphanol		
Traumatic NP	• Gabapentin	• TCA	
		• Botulinum toxin A	

NP = neuropathic pain; TCA = tricyclic antidepressant

[a]Use of duloxetine has similar efficacy to gabapentin and has a low risk of inducing the cardiovascular side effects seen more commonly with TCAs.

[b]Topical lidocaine (patches) may be used as first-line treatment, especially in the elderly population and if there is a concern for central nervous system effects with using other drugs.

[c]Level A evidence Effectiveness demonstrated in various RCTs of good quality. The benefits clearly outweigh risk and burdens

[d]Level B evidence One RCT or more RCTs with methodologic weakness, demonstrate effectivnes. The benefits balanced with risk and burdens

designing a pain regimen for an older adult. Although they share the analgesic effect of acetaminophen, NSAIDs carry additional anti-inflammatory properties.[2] These drugs are available in oral, intramuscular, ophthalmic, and topical formulations and are available both over the counter and by prescription.

Three central categories of adverse effects must be evaluated before NSAID use. Gastrointestinal effects include dyspepsia, bleeding, peptic ulcer disease, and perforation. Adults older than 75 years are at especially high risk for GI complications.[21,31] Use of NSAIDs can also lead to renal impairment through sodium and water retention, electrolyte imbalances, prerenal azotemia, and reduced blood flow to the kidneys. These renal effects, along with the decreased nephron count and renal mass often seen in older adults, can lead to reduced renal blood flow and filtration rates. As people age, their ability to compensate for acid/base, water, and salt imbalances can also become significantly impaired.[28] Finally, although causation has not been established, use of NSAIDs has been linked with increased cardiovascular risks, including hypertension, myocardial infarction, stroke, and death. The NSAIDs also interact with certain medications that are commonly prescribed for older adults (see Table 3 for details).[20,21]

TABLE 3: NSAID Drug/Disease Interactions

Disease State/Medication	NSAID Risk
Disease Interactions	
Congestive heart failure	May worsen heart failure, contraindicated
Ischemic heart disease	Contraindicated
History of GI bleed/high risk for bleed	Increased GI bleeding risk
Age >75 years	Increased GI bleeding risk
Medication interactions	
Anticoagulants	Increased bleeding risk
Antiplatelet agents	Increased bleeding risk
Aspirin	Decreased aspirin antiplatelet activity
Angiotensin-converting enzyme Inhibitors	Decreased blood pressure lowering
Corticosteroids	Increased bleeding risk
Selective serotonin reuptake inhibitors	Increased GI bleeding risk
Alcohol	Increased bleeding risk

GI = gastrointestinal; NSAID = nonsteroidal anti-inflammatory drug.

When prescribing an NSAID to an older adult, specific strategies may be implemented to decrease the risk of side effects. To avoid systemic side effects, alternative administration techniques, such as transdermal patches, gels, and topical solutions, may be beneficial in localized pain.[32,33] Nonoral formulations containing diclofenac have a systemic absorption less than 1/10 that of oral diclofenac.[33] Unfortunately, topical preparations are significantly more expensive than their oral counterparts. To specifically decrease the risk of GI bleeds, oral NSAIDs may also be given with a proton pump inhibitor or misoprostol.[2,34]

The NSAIDs tend to be separated into two broad categories: selective cyclooxygenase-2 inhibitors and nonselective (cyclooxygenase-1 and cyclooxygenase-2) inhibitors. Selective NSAIDs were developed to produce less GI toxicity and platelet inhibition than the nonselective variety.[35] Unfortunately, the selective NSAIDS also have increased cardiotoxic effects and all but two were removed from the market. See Table 4 for a list of selective and nonselective examples.[20]

Two randomized controlled trials demonstrated the improved efficacy of NSAIDs versus acetaminophen in osteoarthritis treatment over periods ranging from 2 to 12 weeks.[22,23] Osteoarthritis Research Society International 2009 guideline updates recognize improved efficacy with NSAIDs versus acetaminophen but warn that the improved efficacy is balanced by an increased adverse effect burden.[30] With respect to short-term pain management, the American Geriatrics Society cites improved efficacy of NSAIDs compared with acetaminophen in the treatment of rheumatoid arthritis, lower back pain, and osteoarthritis.[2] Although there are a variety of recommendations regarding NSAID use among guidelines, one thing that is consistently agreed upon is that when treating older adults with NSAIDs, the smallest dose should be used at a minimal frequency for the shortest duration possible. Long-term use of oral NSAIDs is not a preferred therapy choice in current guidelines.[2,30]

Topicals

Topical medications are often overlooked but provide a unique pathway to control pain that is localized and less likely to be absorbed systemically.[36] This is particularly useful in a person who is already taking many medications as it decreases the likelihood of side effects, decreases drug-drug interactions, and lowers overall pill burden.[37]

Skin integrity must be considered with all topical products. As people age, their skin becomes less hydrated and the epidermal layer thins. The decreased lipid layer makes it more difficult for hydrophilic compounds to penetrate the skin.[36,37] Because of decreased blood flow, doses or frequency may need to be adjusted to compensate for drug reservoir formation.[37]

Available medications include capsaicin, lidocaine, and menthol. Capsaicin is derived from hot peppers and is available over the counter as a cream or by prescription as a highly concentrated patch.[36,38] Over time, capsaicin application desensitizes epidermal nociceptive nerves and decreases substance P.[36,39] If a person can tolerate the burning sensation with application for 1 to 2 weeks, the burning should subside. Capsaicin has been studied in postherpetic neuralgia (PHN), diabetic neuropathy, and osteoarthritis.[40] The capsaicin high-dose patch has been studied in PHN with a pooled number needed to treat of 6– 9 over 12 weeks of application.[41] Additionally, low-dose 0.025%–0.075% creams have consistently shown improvement in pain compared with placebo over 4 to 8 weeks of therapy for PHN, osteoarthritis, and diabetic neuropathy.[42-44] In PHN, continued response for up to 12 months was documented in a study that originally followed patients for 8 weeks. After 8 weeks, 48% had pain relief. Of this group, pain relief continued for 72%.[44]

Lidocaine is available in various cream formulations and as a patch. Lidocaine decreases pain by blocking sodium-ion channels, thereby stopping afferent pain signals.[36] The American Geriatrics Society recommends topical lidocaine for neuropathic pain.[2] The lidocaine patch is applied for 12 hours and removed for 12 hours, potentially making it a poor choice for a person with cognitive impairment who manages his or her own medication. Menthol is also

TABLE 4: NSAID dosing and adjustments

Generic (Brands)	Dosing	Renal/Hepatic Adjustments	Notes
Nonselective			
Aspirin (Bayer®, Bayer Corporation, Kansas City, MO; St. Joseph®, Bedrock Brands LLC, Baltimore, MD)	Analgesic: 325 to 650 mg every 4 to 6 hours up to 4 g/day Anti-inflammatory: 2.4 to 5.4 g/day divided into 4 to 6 doses/day	Renal: CrCl < 10: avoid use 50%–100% dialyzable Hepatic: Severe: avoid use	Available OTC; tablet, chewable, oral powder, suppository Rarely prescribed for analgesia because of the strong antiplatelet effect
Diclofenac (Voltaren®, Novartis Pharmaceuticals, Cambridge, MA; Flector®, Pfizer, Mission, KS; Pennsaid®, Horizon Pharma, Deerfield, IL; Zipsor®, Depomed, Inc., Newark, CA)	Analgesic: 50 mg 3 times daily Rheumatoid and osteoarthritis: 50 mg 3 to 4 times daily	Renal: Avoid use Hepatic: Severe: Reduce dose	Available as tablet, oral powder, topical solution, topical gel, patch, and combined with misoprostol
Etodolac (Lodine®, Wyeth, Collegeville, PA; Lodine XL®, Wyeth, Collegeville, PA)	Analgesic: 200 to 400 mg every 6 to 8 hours Rheumatoid and osteoarthritis: IR: 300 to 500 mg twice daily ER: 400 to 1000 mg once daily	Renal: Severe: avoid use Not dialyzable Hepatic: No adjustment needed	Available as IR and ER tablets
Ibuprofen (Motrin®, Pfizer, Mission, KS; Advil®, Pfizer, Mission, KS)	Analgesic: 200 to 400 mg every 4 to 6 hours Anti-inflammatory: 400 to 800 mg three to four times daily	Renal: Avoid use Hepatic: Use with caution Discontinue if function worsens	Available OTC; tablet, chewable, suspension, gel cap, intravenous
Indomethacin (Indocin®, Merck & Company, Inc., Whitehouse Station, NJ)	Analgesic: 20 to 40 mg 3 times daily Anti-inflammatory: 25 to 50 mg 2 to 3 times daily	Renal: Severe: avoid use Hepatic: Use with caution	Primarily used in gout Available as IR and ER tablets
Ketoprofen (Oruvail®, Wyeth, Collegeville, PA; Orudis®, Wyeth, Collegeville, PA)	Analgesic: 25 to 50 mg every 6 to 8 hours Rheumatoid arthritis or osteoarthritis: 50 mg 4 times daily, or 75 mg 3 times daily (maximum 300 mg/day)	Renal: Mild: Maximum of 150 mg/day Glomerular filtration rate <25: Maximum 100 mg/day Hepatic: Maximum initial dose: 100 mg/day	Available as tablet Limit dose to 100 mg/day in patients with albumin <3.5 g/dL
Ketorolac (Toradol®, Roche Pharmaceuticals, Nutley, NJ)	10 mg every 4 to 6 hours (maximum daily dose 40 mg)	Renal: Same as geriatric dosing. Severe: avoid use Hepatic: May cause liver function test elevation Discontinue if patient shows signs of liver disease	Available as tablet, intravenous, and intramuscular; Use limited to 5 days; Increased risk for gastrointestinal bleed in geriatric patients
Nabumetone (Relafen®, GlaxoSmithKline, Philadelphia, PA)	Rheumatoid arthritis and osteoarthritis: 1000 mg/day in 1 or 2 divided doses Maximum dose <50 kg 1000 mg/day maximum dose >50 kg: 2000 mg/day	Renal: CrCl 30–49: 750 mg/day CrCl <30: 500 mg/day Hepatic: Severe: may be less effective	Available as tablet

TABLE 4: NSAID dosing and adjustments (continued)

Generic (Brands)	Dosing	Renal/Hepatic Adjustments	Notes
Naproxen (Naprosyn®, Roche, Nutley, NJ; Anaprox®, Roche, Nutley, NJ; Aleve®, Bayer Corporation, Kansas City, MO)	Analgesic: 220 to 500 mg twice daily Gout: 750 mg loading dose, then 250 mg 3 times daily until flare subsides	Renal: Avoid use Hepatic: Use caution; dose reductions recommended	Available OTC; 200 mg of naproxen = 220 mg of naproxen sodium
Oxaprozin (Daypro®, Pfizer, Mission, KS)	Rheumatoid arthritis and Osteoarthritis: 1200 mg once daily.	Renal: Severe: 600 mg/day Dialysis: 600 mg/day Hepatic: Severe: use caution	Available as a tablet Low body weight: start at 50% of usual dose
Piroxicam (Feldene®, Pfizer, Mission, KS)	Rheumatoid arthritis and Osteoarthritis: 10 to 20 mg/day in 1 or 2 divided doses	Renal: Severe: avoid use Hepatic: Use lowest possible dose	Available as capsule
Sulindac (Clinoril®, Merck & Company, Inc., Whitehouse Station, NJ)	Analgesic/Gout: 200 mg twice daily Osteoarthritis: 150 mg twice daily	Renal: Severe: avoid use Hepatic: Discontinue if abnormal liver function test	Available as tablet
Semiselective			
Meloxicam (Mobic®, Boehringer Ingelheim Pharmaceuticals, Inc., St. Joseph, MO)	Osteoarthritis: 7.5 mg once daily to maximum of 15 mg/day	Renal: CrCl <20: avoid use Hemodialysis: Maximum 7.5 mg/day Hepatic: Severe: Insufficient data	Available as tablet COX-2 >>> COX-1
Selective			
Celecoxib (Celebrex®, Pfizer, Mission, KS)	Rheumatoid arthritis and Osteoarthritis: 100 to 200 mg twice daily Gout: 400 mg twice daily	Renal: Severe: Avoid use Hepatic: Moderate: 50% dose reduction Severe: avoid use	Available as capsule COX-2 only Exposure may be increased in geriatric patients; start at lowest possible dose

COX = cyclooxygenase; CrCl = creatinine clearance; ER = extended release; IR = immediate release; OTC = over the counter

available in many creams and patches over the counter. Through counterirritant effects, it causes a cooling sensation along with pain relief.[36,45]

With all topical medications, patients should be instructed to not apply the medication to open skin or apply heat to the area as this may increase systemic absorption.[39] Current clinical evidence regarding the use of topicals has allowed the use of other pain medications in addition to topicals. Randomized controlled trials of topicals as monotherapy do not exist, so topicals should be viewed as an ideal add-on agent for an older adult with localized whose pain is uncontrolled with other medications.

Adjuvants

Adjuvant pain medications are those that are not typically used for pain but may be helpful for its management. Agents may be used alone; however, effects are enhanced when used in combination with other analgesics. Currently, only two non-opiate adjuvant therapies are approved by the US Food and Drug Administration for the treatment of neuropathic pain: pregabalin and duloxetine.

TABLE 5: Common medications for neuropathic pain

Medication	Starting Dose	Dose Range	Indications	Common Side Effects
Pregabalin (Lyrica, Pfizer, Mission, KS)	150 mg/day (split BID-TID)	150–300 mg/day (split BID-TID)	Diabetic peripheral neuropathy Fibromyalgia Spinal cord injury Postherpetic neuralgia	Peripheral edema, weight gain, dizziness, somnolence, asthenia, headache, dry mouth
Gabapentin (Neurontin, Pfizer, Mission, KS)	300 mg (split TID)	1800–3600 mg (split TID)	Postherpetic neuralgia Fibromyalgia	Peripheral edema, weight gain, dizziness, somnolence, asthenia, headache, dry mouth, concentration disorders
Amitriptyline (Elavil, AstraZeneca, North Wilmington, DE)	10–25 mg daily	75–150 mg daily	Unlabeled use	Dry mouth, constipation, sedation, weight gain, sexual dysfunction, electrocardiogram changes
Nortriptyline (Pamelor, Mallinckrodt Pharmaceuticals, Dublin, Ireland)	10–25 mg daily	75–150 mg daily	Unlabeled use	Dry mouth, constipation, sedation, weight gain, sexual dysfunction, electrocardiogram changes
Duloxetine (Cymbalta, Eli Lilly and Company, Indianapolis, IN)	30–60 mg daily	60–12 omg daily	Diabetic peripheral neuropathy Fibromyalgia Chronic musculoskeletal pain	Somnolence, fatigue, headache, diarrhea, constipation, nausea, dry mouth, dizziness, insomnia
Venlafaxine extended release (Effexor XR, Pfizer, Mission, KS)	37.5 mg daily	75–225 mg daily	Unlabeled use	Headache, insomnia, drowsiness, dizziness, diaphoresis, nausea, elevated blood pressure, anxiety, agitation
Lamotrigine (Lamictal, GlaxoSmithKline, Philadelphia, PA)	50 mg/day	200–600 mg/day	Unlabeled use	Nausea, edema, insomnia, agitation, Stevens-Johnson syndrome
Carbazepine (Tegretol, Novartis, Cambridge, MA)	200 mg/day (split BID)	400–800 mg/day	Trigeminal neuralgia	Elevated blood pressure, dizziness, drowsiness, headache, agitation, nausea, constipation, vomiting
Oxcarbazepine (Trileptal, Novartis, Cambridge, MA)	300–600 mg/day (split BID)	1500–1800 mg (split BID)	Unlabeled use	Dizziness, drowsiness, headache, vomiting, abnormal gain, diplopia, nystagmus

BID = twice a day; TID = three times a day.

Persons with neuropathic pain, fibromyalgia, and refractory persistent pain are ideal candidates for adjuvant analgesics.[46] A causative relationship has been identified between chronic pain and depression in that depression may intensify patient sensitivity to pain.[47,48] Therefore, agents such as duloxetine specifically may have a synergistic effect in older adults who experience depression along with chronic pain.

Antidepressants have consistently shown benefit in the treatment of painful diabetic neuropathy, with a number needed to treat between 2.1 and 5.5 to achieve 50% reduction in pain.[49,50] Tricyclic antidepressants (TCAs) are commonly used as an adjuvant therapy for neuropathic and chronic pain. Amitriptyline and other TCAs can be dosed once daily and are inexpensive. The mechanism is believed to work through the inhibition of neurotransmitter reuptake in the synaptic cleft.[51] Despite having the strongest evidence for neuropathy-related pain relief, in older adults this class should be avoided because of the higher risk for adverse effects, such as anticholinergic effects and cognitive impairment.[31]

Because of the profound anticholinergic effects and risk for cardiotoxicity that can be caused by TCA class, exploration across the antidepressant spectrum widened for other drugs that may have similar efficacy. Serotonin-norepinephrine reuptake inhibitors, such as venlafaxine and duloxetine, reuptake both serotonin and norepinephrine by increasing the neurotransmitters. The drugs dampen pain signals to the brain, are generally well tolerated by older adults, and have fewer side effects compared with TCAs. Venlafaxine has been studied for analgesia with pain relief at higher doses ranging up to 225 mg/day. Unfortunately, increased hypertensive episodes have also been noted at these doses.[52] The practicality of venlafaxine as an adjunctive agent in neuropathic pain or dual therapy for depression is limited for older adults. Conversely, duloxetine does not have similar effects on blood pressure and is noted to reduce painful diabetic neuropathy by 50% compared with placebo.[29] This places it as the preferred serotonin-norepinephrine reuptake inhibitor for older adults who require adjunctive therapy. In addition to antidepressant therapy, antiepileptics are increasingly being used in the symptomatic management of several neuropathic pain disorders.[53]

Gabapentin is a modulator of the alpha-2-delta subunit of the calcium channels in the central nervous system, accounting for antinociceptive and antiepileptic effects. Although not indicated for neuropathic pain by the US Food and Drug Administration, gabapentin is one of the few drugs that has demonstrated efficacy in treatment of diabetic neuropathic pain and shows similar efficacy to pregabalin with a number needed to treat of 3.9–4.2.[54-56] At this time there are no head-to-head trials comparing efficacy and safety.[17,55,56] Most trials have evaluated pregabalin versus gabapentin with respect to cost-efficacy or gabapentin refractive standpoint. This is an important item for many older adults who are living on a tight budget and have a strict formulary policy with their respective insurance company. Accessibility can also be a limitation for older adults as pregabalin is classified as a controlled substance, which consequently reduces the ease of prescription refilling and pickup. Other considerations for this class include the possibility for renal adjustment and the increased risk for falls secondary to sedation and dizziness.[53] For antidepressants and antiepileptics, therapy should begin with the lowest possible dose and increase slowly based on response and side effects, keeping in mind the caveat that some agents have a delayed onset of action and therapeutic benefits are slow to develop. In addition, an adequate therapeutic trial should be conducted before discontinuing a seemingly ineffective treatment. It is important to note that adverse events are likely to occur with central nervous system medications, especially in older adults. See Table 5 for a list of common medications used for neuropathic pain and their respective side effects. [20]

Choosing the Right Agent

When designing a pain management regimen in an older adult, the choice of therapy should be tailored to a particular patient. As described earlier, an assessment of a person's pain should be done with a thorough history that will guide treatment options. In addition to the report of pain, an assessment of the patient's comorbidities, other medications, and overall functional status should be completed to guide the prescriber in choosing the best medication.[4]

Weighing the potential risks and benefits of medication options should be done with the patient or caregiver to design a patient-centered regimen. Starting with one medication is ideal in an older adult to fully assess efficacy of the medication and link side effects to the correct medication. If one medication is inadequate, adding a medication from a different class may be beneficial.[2,4] Taking into consideration the frail state of older adults is critical in making the most appropriate choice for pain management.

Throughout this article we have outlined some of the most common non-opiate options for older adults that may be considered for monotherapy or as adjunctive agents. As mentioned previously, no medication is without risk or benefit, therefore several considerations for non-opiate treatments have been discussed with the goal of highlighting new options that prescribers may use with older adults. Pain management remains an important part of patient-centered care across the spectrum of disciplines and a critical part of improving the quality of life for older adults.

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