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Pharmacotherapies in Geriatric Chronic Pain Management

Zachary A. Marcum, PharmD, PhD[a], **Nakia A. Duncan, PharmD**[b], and **Una E. Makris, MD, MSc**[c,*]

[a] Department of Pharmacy, University of Washington School of Pharmacy, 1959 Northeast Pacific Avenue, Box 357630, Seattle, WA 98195, USA

[b] Texas Tech University Health Sciences Center School of Pharmacy, 4500 South Lancaster Street, Building 7, Room 215, Dallas, TX, USA

[c] Division of Rheumatic Diseases and the VA North Texas Health Care System, Department of Internal Medicine, UT Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, TX 75390-9169, USA

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Pain is highly prevalent, costly, and frequently disabling in later life.[1–6] It is most often owing to musculoskeletal causes,[7] usually involves multiple sites,[8] and rarely occurs in the absence of other comorbidities.[9] Consistent with other geriatric syndromes, chronic pain in older adults often develops via a multifactorial pathway, resulting in various sequelae including poor self-reported health and quality of life, disability, impaired ambulation, depression, and decreased socialization, as well as falls, low energy, and impaired sleep.[6,10–13]

CHALLENGES TO MANAGING PAIN IN LATER LIFE

Barriers to managing chronic pain effectively in older populations[14] include a limited evidence base to guide management,[15] lack of health care professional education,[16] health care professionals' concerns about the potential for treatment-related harm,[17] and older adults' beliefs about pain and pain treatments.[18] Other barriers specific to geriatric populations include age-related physiologic changes resulting in altered drug absorption and decreased renal excretion, sensory impairments, polypharmacy, and multimorbidity.[15] There is limited evidence in the literature to guide pharmacologic management because older adults are often underrepresented or excluded from clinical trials.[15,19–21] More specifically, the presence of multiple comorbid conditions such as[22] cognitive impairment, gait disorders, and kidney, lung, and cardiovascular disease often serve as exclusion criteria in drug trials. Further, it is important to recognize that the pain experience, values, and priorities may be

* Corresponding author. una.makris@utsouthwestern.edu.

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different among older adults as compared with younger adults,[23–25] and that it is not appropriate to use a “one size fits all” approach when applying guidelines from younger to older populations.

EXISTING GUIDELINES FOR MANAGING CHRONIC PAIN IN LATER LIFE

Two guidelines and several consensus statements provide useful information regarding the assessment and management of chronic pain in older adults (Appendix 1 lists additional resources).[10,26–29] The American Geriatrics Society guideline (last updated in 2009) provides recommendations on the initiation and titration of commonly used pharmacotherapies.[28,29] Given the complexity of managing older adults with chronic pain, experts agree that these patients are most likely to benefit from an interdisciplinary team approach. This team may consist of various health care providers, including those in primary care, gerontology, geriatrics, rheumatology, physical medicine and rehabilitation, physical and occupational therapists, pharmacy, nursing services, social work, and psychiatry/psychology. There is agreement across guidelines about the need to intervene aggressively using an interdisciplinary approach that includes both pharmacologic and nonpharmacologic treatments. Pain relief is one of the most commonly endorsed goals of older adults.[30] To achieve this goal, collaborative care approaches have been found to be effective. One randomized controlled trial found that a collaborative multicomponent intervention that included physician and patient education, activation, and symptom monitoring in targeted primary care patients with chronic pain was associated with significant improvement in pain-related disability, pain intensity, and depressive symptom scores over a 12-month period.[31]

In this article, we provide a review of nonopioid pharmacotherapies for chronic pain management in older adults. The safety and efficacy of opioids for the treatment of noncancer pain is covered by Dr. Naples and colleagues (See, “The Role of Opioid Analgesics in Geriatric Pain Management,” in this issue).

Specific Pharmacologic Agents

Topicals—Topical medications provide a unique pathway to control pain that is localized and less likely to be absorbed systemically.[32,33] This route of administration is particularly important for older adults who often take multiple medications, because it decreases the likelihood of side effects, drug–drug interactions, and overall pill burden.[33] However, skin integrity must be considered with all topical products. With age, the skin becomes less hydrated and the epidermal layer thins. Absorption of topical medications can be affected by decreased hydration, tissue thickness, and surface lipids on the skin. The decreased lipid layer makes it more difficult for transdermal medications (eg, lidocaine patches) to penetrate the skin, because they are designed for gradual absorption and rely on intact, well-hydrated skin with adequate circulation. Dry or thin skin without a good subcutaneous layer can inhibit absorption of the drug potentially leading to an overtreatment or undertreatment effect.[32,33] In addition, owing to decreased blood flow, doses or frequency may need to be adjusted to compensate for drug reservoir formation.[33]

Available topical medications include menthol, capsaicin, lidocaine, and diclofenac; **Table 1** details the indications, dose ranges, formulations, and clinical pearls for topical analgesics.

Menthol/Methyl Salicylate—Menthol is available in many creams and patches over the counter. It causes a cooling sensation along with pain relief via counterirritant effects.[34] Menthol products are ideal for older adults (often used as adjunctive therapy) to treat minor pains because they have minimal side effects.

Capsaicin—Capsaicin is derived from hot peppers and is available over the counter as a cream or by prescription as a highly concentrated patch.[32,35] Over time, capsaicin application desensitizes epidermal nociceptive nerves and decreases substance P, leading to pain reduction.[32,36] If an individual can tolerate the burning sensation with application for 1 to 2 weeks, the burning usually subsides. Capsaicin has been studied in patients with postherpetic neuralgia (PHN), diabetic neuropathy, and osteoarthritis (OA).[37] The high-dose patch, Qutenza, has been studied in PHN with a pooled number needed to treat of 6 to 9 over 12 weeks of application (median age of participants across trials was 71 years).[38] Additionally, low-dose (0.025% to 0.075%) creams have consistently shown improvement in pain compared with placebo over 4 to 8 weeks of therapy for PHN, OA, and diabetic neuropathy.[39–41] 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% of participants.[41]

Lidocaine—Lidocaine is available in various cream formulations and as a patch. Lidocaine decreases pain by blocking sodium ion channels, thereby stopping afferent pain signals.[32] The American Geriatrics Society recommends topical lidocaine for neuropathic pain.[29] The lidocaine patch is applied for 12 hours and removed for 12 hours, making it a poor choice for a cognitively impaired individual managing his or her own medications.

Topical Diclofenac—Widely used for more than 30 years outside of the United States, topical diclofenac sodium was the first topical NSAID approved by the US Food and Drug Administration (FDA) in 2007. It is often used for knee or hand OA-related pain. The literature on topical NSAIDs for sports injuries, musculoskeletal pain, or inflammatory arthritis has focused on subjects younger than 65 years old.[42,43] Available data suggest that some topical NSAIDs have comparable, or somewhat lower, efficacy than oral NSAIDs.[44,45] Even if less effective, these agents may be a reasonable option because their safety profile is superior to that of oral NSAIDs.[46] A systematic review of the literature evaluated safety of topical NSAIDS in older adults (age >60 years old) and showed that topical NSAIDs are almost as effective and carry a lower risk of severe adverse effects (gastrointestinal [GI]) as compared with oral NSAIDs.[47] There are limited data in older adults with baseline renal impairment or who are anticoagulated to understand potential adverse events of topical NSAIDS in these populations. Patients should be counseled that topical NSAID users have reported non–life-threatening GI events and many application site adverse events; thus, they are not entirely without risk.

General Considerations—With all topical medications, patients should be instructed to not apply the medication to open skin or apply heat to the area because this may increase

systemic absorption. Topical agents are considered an ideal adjunct agent for an older adult with localized pain that is uncontrolled with other medications (or if specific classes of medications are contraindicated). Of note, care should be taken when disposing patches to avoid the unintentional consumption by children or pets (see **Table 1**).

Acetaminophen—The analgesic activity of acetaminophen (APAP) results from the central inhibition of prostaglandin synthesis. Yet, the primary mechanism of prostaglandin synthesis inhibition by APAP remains unknown.[48] Several studies have investigated the pharmacokinetic properties of APAP in healthy older adults and have reported varying effects of age.[48] APAP is rapidly and completely absorbed from the GI tract, and neither the rate nor the extent of absorption seems to be age dependent.[48] The volume of distribution decreases with age and female sex, which is consistent with the drug's hydrophilic nature as well as age-associated changes in body composition; no differences have been reported in the volume of distribution between healthy and frail older adults.[48] In general, advanced age does not alter the clearance of APAP, which is metabolized by phase II hepatic conjugative metabolism. However, some studies suggest that the metabolism of APAP in older adults is greatly variable and that the intrinsic conjugative activity of the liver may be preserved in healthy older adults but may be compromised in the frail elderly. It is unknown whether these changes in pharmacokinetic properties are responsible for increases in APAP hepatotoxicity.

APAP is recommended as a first-line analgesic for mild-to-moderate pain owing to OA of the knee and hip in multiple guidelines.[48] However, mounting evidence of its limited effectiveness (compared with placebo and other analgesics) and growing safety concerns have shifted opinions in recent years.[49–52] For example, the comparative effectiveness of available treatments for knee OA were evaluated in a systematic review and network metaanalysis.[50] Included studies were randomized trials of adults with knee OA comparing 2 or more of the following: APAP, diclofenac, ibuprofen, naproxen, celecoxib, intraarticular (IA) corticosteroids, IA hyaluronic acid, oral placebo, and IA placebo. A total of 137 studies comprising 33,243 participants were included, and 3-month outcomes of pain, function, and stiffness were assessed as the primary outcomes. The median age of participants across trials was 62 years. For pain, all interventions were statistically significantly better than oral placebo, with effect sizes ranging from 0.18 for the least efficacious treatment (APAP) to 0.63 for the most efficacious treatment (IA hyaluronic acid). Moreover, all treatments except APAP met the prespecified criteria for a clinically significant improvement in pain. Compared with APAP, naproxen, ibuprofen, diclofenac, IA hyaluronic acid, and IA corticosteroids were significantly superior for pain control. However, celecoxib was not found to be significantly better than APAP. For function, naproxen, ibuprofen, diclofenac, and celecoxib were significantly better than APAP. In terms of safety, oral nonselective NSAIDs led to more GI adverse events and withdrawals owing to adverse events than oral placebo and APAP, whereas these events were similar between APAP and celecoxib.

Another study was conducted using a systematic review and metaanalysis of placebo-controlled randomized trials to examine the efficacy and safety of APAP in the management of low back pain and OA of the hip or knee.[51] Thirteen randomized trials were included, and the investigators reported that there was "high-quality" evidence (based on the GRADE

criteria) that APAP is ineffective for reducing pain intensity and disability or improving quality of life in the short term in people with low back pain. For hip or knee OA, there was "high-quality" evidence that APAP has a significant, although not clinically important, effect on pain and disability in the short term. More specifically, APAP was found to have a small effect (ie, <4 points on a 0–100 point scale) on pain, which is not likely to be meaningful for patients or their clinicians. In addition, the number of patients reporting any adverse events was similar in the APAP and placebo groups. In summary, this study found APAP to be ineffective for the treatment of low back pain and to provide a minimal short-term benefit for people with OA. The authors suggested that these results should lead to a reconsideration of APAP being a first-line treatment in clinical practice guidelines for low back pain and hip or knee OA.

Finally, a systematic review assessed the adverse event profile of APAP in the general adult population.[52] Eight cohort studies were included, and the main outcomes examined were all-cause mortality, cardiovascular adverse drug events (incident myocardial infarction, cerebrovascular accident, and hypertension), GI bleeding, and renal (reductions in estimated glomerular filtration rate, increases in serum creatinine, and need for renal replacement therapy) events. Given the known limitations of observational data (eg, confounding by indication), the results demonstrated a consistent dose-response association between APAP at standard analgesic doses and adverse drug events that are often observed with NSAIDs. For example, this review reported a dose–response association between APAP and increasing incidence of mortality, cardiovascular, GI, and renal adverse drug events. Furthermore, given the risk of APAP overdose, new regulations went into effect in 2014 that decreased the amount of APAP allowed in prescription products from 500 to 325 mg.[53] These new regulations do not include over-the-counter products.

Whereas prior and current guidelines recommend APAP as first-line therapy for the treatment of OA in older adults, recent evidence of uncertain analgesic benefit and increased safety concerns suggest a shifting risk–benefit profile.[54] Until further evidence becomes available, clinicians should continue evaluating the risk versus benefit when prescribing APAP using patient-specific information. Known risk factors for APAP-related adverse drug events, such as a renal impairment, hepatic dysfunction, and alcohol abuse, should be considered, and adequate dosing trials should be attempted before discontinuing APAP. Because APAP is the most commonly used analgesic and is available over the counter, patient education is important to communicate the known risks and benefit[53] (**Table 2**).

Nonsteroidal antiinflammatory drugs—NSAIDs are one of the most common classes of drugs used to treat chronic pain owing to OA and other musculoskeletal disorders in older adults.[55–57] Specifically, an estimated 40% of the population age 65 years and older fill one or more prescriptions for an NSAID each year.[58] Considering that NSAIDs are also currently available over the counter, it is assumed that an even greater number of older adults in the United States take NSAIDs in an effort to relieve their pain. Although these agents can be effective in treating inflammation and pain, older adults are at increased risk for adverse drug events owing to age-related loss of physiologic organ reserve, increased comorbidities, polypharmacy, and changes in pharmacokinetics.[29] As a result, NSAID use causes an estimated 41,000 hospitalizations and 3300 deaths each year among older adults.[56] Some

specific adverse drug events of concern with chronic use of NSAIDs include GI, renal, cardiovascular, cerebrovascular, and central nervous system (CNS) adverse effects.[59]

Two of the most serious adverse drug events associated with NSAID use are serious GI bleeds and cardiovascular events, such as myocardial infraction and stroke.[60] In 2005, the FDA issued a warning that NSAID use could cause heart attacks and strokes that could lead to death.[60] To help minimize these risks, the FDA also issued a public health advisory stating that "NSAIDs should be administered at the lowest effective dose for the shortest duration consistent with individual patient treatment goals."[61] Moreover, in 2015 the FDA strengthened this warning, based on a comprehensive review of new safety information, stating that all prescription NSAID labels need to contain information on the risk of heart attack and stroke.[61,62] Continued pharmacovigilance research is needed to better describe the comparative efficacy and safety of NSAID use in older adults.

Given the concerns of adverse drug events, NSAIDs are included throughout the updated 2015 American Geriatrics Society Beers Criteria for Potentially Inappropriate Medication Use in Older Adults.[63] The non–cyclooxygenase-selective NSAIDs are included as a medication class to avoid owing to their increased risk of GI bleeding or peptic ulcer disease in high-risk groups, including those aged greater than 75 years or taking oral or parenteral corticosteroids, anticoagulants, or antiplatelet agents. The recommendation is to avoid chronic use, unless other alternatives are not effective and the patient can take a gastroprotective agent (proton pump inhibitor or misoprostol). Indomethacin is specifically called out for its greater risk of adverse CNS effects. Moreover, NSAIDs (including cyclooxygenase-2 inhibitors) are listed as a drug–disease interaction to avoid in older adults with heart failure and chronic kidney disease (creatinine clearance <30 mL/min). Finally, NSAIDs are listed as having clinically important drug–drug interactions with corticosteroids (oral or parenteral) and warfarin owing to an increased risk of peptic ulcer disease and bleeding.

One approach to reducing adverse drug events associated with NSAIDs is to avoid the use of specific agents that are known to interact with NSAIDs and use preferred alternative analgesics (eg, topicals, APAP), sometimes in combination. This is particularly important in older adults with preexisting hypertension, chronic kidney disease, heart failure, and/or peptic ulcer disease, or those taking concomitant warfarin or corticosteroids. If NSAID use is not contraindicated, a trial (eg, 1–2 weeks in duration) of analgesic dosing of a nonacetylated salicylate (eg, salsalate) or ibuprofen or celecoxib may be acceptable.[64] For those with moderate to moderately severe OA pain, a trial of a low-dose opioid or an opioidlike agent (eg, codeine, tramadol) in combination with APAP is another option. The rationale for this approach is to combine 2 different mechanisms of analgesic action. In those older adults who require chronic NSAIDs, a proton pump inhibitor or misoprostol should be used to avoid the risk of peptic ulcer disease.[64] Until further research and guidelines are published on the use of NSAIDs in older adults, clinicians and patients should practice shared decision making to minimize potential risk and maximize patient outcomes from NSAID use (**Table 3**).

Adjuvant Therapies—Adjuvant pain medications are those that are not typically used as first-line agents 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 there are only 2 nonopiate adjuvant therapies approved by the FDA for the treatment of neuropathic pain: pregabalin and duloxetine. Neuropathic pain is characterized by chronic pain, and results from various heterogeneous diagnoses/etiologies (ie, diabetic peripheral neuropathy, postherpetic neuralgia, central post stroke pain, phantom limb pain).[65,66] Therefore, individuals with neuropathic pain and refractory persistent pain whose neuropathic pain is not well-managed with conventional therapies are ideal candidates. As discussed in another section of this series (see Christopher Eccleston and colleagues' article, "Psychological Approaches in Geriatric Pain Management," in this issue), older adults with chronic pain have a substantially increased risk for depression and that depression may intensify a patient's sensitivity to pain.[67,68] Thus, antidepressant use may have synergistic effects in older adults experiencing depression along with chronic pain.[69]

Antidepressants—The mechanism for how antidepressants are effective in pain management is not fully known; however, these medications work through the inhibition of neurotransmitter (ie, serotonin and norepinephrine) reuptake in the synaptic cleft,[70] particularly along the descending spinal pain pathways.[66] It is also believed that antidepressants may exert adjunctive therapeutic effects via histamine receptors and sodium channels.[71] Several antidepressants are efficacious in the management of chronic neuropathic pain, including the tricyclic antidepressants, particularly tertiary amine subtypes, such as amitriptyline, nortriptyline, and doxepin. Despite having the strongest evidence for neuropathy-related pain relief, this class should be avoided in older adults if possible owing to increased risk for adverse effects such as anticholinergic effects and cognitive impairment.[63]

Serotonin–norepinephrine reuptake inhibitors, such as venlafaxine and duloxetine, are mixed acting antidepressants that predominately inhibit serotonin reuptake at low doses and norepinephrine reuptake at high doses, thus increasing these neurotransmitters and dampening pain signals to the brain. Serotonin–norepinephrine reuptake inhibitors are generally well-tolerated by older adults and have fewer side effects compared with tricyclic antidepressants.[72] Venlafaxine has been studied for analgesia with pain relief occurring at higher doses ranging up to 225 mg/d. In a study by Rowbotham and colleagues,[73] 56% of the participants receiving venlafaxine 150 to 225 mg achieved at least a 50% reduction in pain intensity versus 34% of participants in the placebo group. The number needed to treat for an additional beneficial outcome in reduction of pain intensity was 4.5.[73,74] Unfortunately, increased hypertensive episodes have also been noted at these doses. Therefore, the practicality of venlafaxine as an adjunctive agent in neuropathic pain or dual therapy for depression may be limited in older adults.[72] Conversely, duloxetine does not have such effects on blood pressure and is noted to reduce diabetic peripheral neuropathic pain (DPNP) by 50% as compared with placebo.[75]

Antiepileptics—Anticonvulsants, initially indicated for epileptic seizures with a variety of mechanisms of action, have been shown to be effective at treating various chronic pain

conditions, in particular neuropathic pain.[76] Carbamazepine is a prototypical anticonvulsant that blocks voltage-sensitive sodium channels, resulting in the stabilization of hyperexcited neural membranes and inhibition of repetitive firing or reduction of propagation of synaptic impulses.[76] In several studies, carbamazepine has shown efficacy in the treatment of trigeminal neuralgia; however, its use is complicated by pharmacokinetic factors and frequent adverse effects. Within the guidelines for the treatment of neuropathic pain, carbamazepine is listed as a first-line therapy alongside oxcarbazepine, which is noted to have a better side effect profile. However, there are no controlled trials documenting a beneficial effect of oxcarbazepine for trigeminal neuralgia and thus it carries and off-label indication for neuropathic pain.[76,77] If a patient is unable to tolerate carbamazepine, it is reasonable to consider a trial of lamotrigine, which also has shown efficacy in trigeminal neuralgia by stabilizing sodium channels and suppressing the release of glutamate.[76]

Gabapentin and pregabalin are modulators of the alpha-2-delta subunit of the calcium channels in the CNS, accounting for antinociceptive and antiepileptic effects. Gabapentin is indicated for PHN; although not FDA indicated in the treatment of DPNP, it has demonstrated efficacy for this condition and is widely used in clinical practice.[77–79] Gabapentin shows similar efficacy in pain reduction to pregabalin, with a number needed to treat of 3.9 to 4.2; however, pregabalin is FDA indicated for PHN, DPNP, and fibromyalgia.[80,81] In a study conducted in older adults (mean age 66 years), both anticonvulsants have consistently shown improvement in mood, sleep disturbance, and quality of life.[79] When compared with antidepressants such as duloxetine and amitriptyline on the primary outcome of subjective pain, there is no difference among treatment groups (amitriptyline, duloxetine, pregabalin) in the reduction of pain severity.[79] In a study[82] comparing duloxetine versus pregabalin versus duloxetine and gabapentin in patients (mean age, 61 years) with DPNP, there were no between-group differences with respect to treatment emergent events (including nausea, vomiting, insomnia, peripheral edema, hyperhidrosis, or decreased appetite). Insomnia was reported more frequently in the pregabalin and gabapentin groups.[82] In the older adult population, there was an increased risk for falls with the use of gabapentin and pregabalin owing mainly to the side effects of dizziness and somnolence. Of note, the 2015 AGS Beers Criteria[63] identify both agents as potentially inappropriate medications in older adults with a history of falls or fractures (unless being used for the treatment of seizure or mood disorders). The updated criteria recommend increased monitoring with renal impairment. Because both agents are primarily excreted renally, dose adjustment should be considered as renal function declines[63] (**Table 4**).

Muscle Relaxants—Skeletal muscle relaxants include a variety of agents that are separated into 2 categories: antispasticity agents and antispasmodics.[83] Each of these categories has different indications, mechanisms of action, and side effect profiles. Antispasticity agents work on the spinal cord or directly on the skeletal muscle to improve hypertonicity and involuntary spasms. These medications are used for spastic conditions such as cerebral palsy, multiple sclerosis, spinal cord injuries and after cerebrovascular accidents; this category of medications should be used with caution in older adults with chronic pain due to degenerative or neuropathic pain. The use of skeletal muscle relaxants

among older adults is associated with sedation and confusion, which may lead to an increased risk of falls and injuries.[84] Per the 2015 Beers criteria, muscle relaxants (including cyclobenzaprine, carisoprodol, methocarbamol, and metaxolone) are considered as being high-risk medications in older adults due to anticholinergic adverse drug effects, excessive sedation, and weakness; however, they continue to be used among older adults.[63] Further, a recent retrospective cohort study in older (>65 years of age) Veterans showed that muscle relaxants (including methocarbamol and cyclobenzaprine, among others) were associated with increased risk for emergency department visits as well as all-cause hospitalizations (including those for falls and fractures).[85] Another commonly used agent used for spasticity, and not included in the Beer's criteria, is baclofen. Baclofen is a centrally acting skeletal muscle relaxant with an FDA indication to treat spasticity related to CNS lesions; dosing regimens vary by indication. Among the antispasticity agents, baclofen is generally well-tolerated with a decreased occurrence of CNS depression. Dantrolene is another agent that works peripherally to increase the release of calcium from the sarcoplasmic reticulum in the skeletal muscle cell thus slowing contraction cycles. However, use of dantrolene is limited by the risk of hepatotoxicity with chronic use. Last, tizanidine is a centrally acting alpha 2-adrenergic agonist that increases the inhibition of presynaptic motor neurons with no direct effect on muscle fibers. Similarly, its use in older adults is limited by dose-dependent adverse drug events, drug–drug interactions, and the possibility of prolonged QT intervals (**Table 5**).

New Analgesics in the Pipeline

The medication classes discussed in this article are traditionally known to be first-, second-, or third-line agents for chronic pain. There are many new agents and compounds in varying stages of development/testing for the treatment of chronic pain. At this time, it is premature to predict the potential role of these newer medications for chronic pain management in older adults. In the absence of new safe and effective analgesics, the primary focus is to trial existing therapies, in different combinations, and with different multidisciplinary approaches to maximize pain relief and minimize medication toxicity.

Making a Plan: Approach to Managing Chronic Pain in Older Adults with Pharmacologic Agents

Expectations and treatment goals—"Success" is determined largely by what the patient and provider determine are the treatment goals.[69] The older adult should be encouraged to communicate his/her expectations for pain relief. The field of pain management is moving away from solely assessing and managing a pain intensity score (eg, a 0–10 numeric rating score) and toward understanding and targeting the functional outcomes and personal (realistic) goals that older adults would like to achieve.

Monitoring and managing medication adjustments for older adults—The clinical challenge is how to manage pain effectively and safely in older adults. Many older adults have already tried several classes of medications and may be hesitant to attempt a trial of a new medication or a combination of analgesics. Using 2 or more analgesic medications with complementary mechanisms of action may lead to greater pain relief with less toxicity as opposed to higher doses of a single pain medication. Starting 1 medication at a time is a

preferred strategy to better evaluate effect and safety. Several strategies may help providers to achieve success when recommending new analgesic trials or combinations of therapy:

- Be prepared to respond to questions and concerns for each medication or combination thereof;
- Provide potential options for “rescue” pain medications during trials of new medications;
- Be available to listen to and be receptive to the patients’ concerns;
- Avoid communicating guarantees of positive results;
- Emphasize the need for adherence to the instructed regimen;
- Encourage the patient to call if new concerning signs or symptoms develop after starting the medication;
- Develop a careful surveillance plan to determine whether treatment goals are being met and for monitoring potential toxicity; and
- If goals are not met, consider tapering and discontinuing medication.[10,29]

To achieve patient identified therapeutic goals (including reduction in pain intensity and pain related disability) with pharmacologic (and/or nonpharmacological) management, employing a multidisciplinary approach is paramount. Thus, successful pain management in older adults requires a collaborative approach among all members of the health care team. Finally, combining pharmacologic and nonpharmacological (including activity based, psychological) interventions is likely to have the highest yield for improving pain control in older adults.

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APPENDIX 1

RECOMMENDED RESOURCES FOR PHARMACOLOGIC MANAGEMENT OF CHRONIC PAIN IN OLDER ADULTS

Resource	Content	Origin	Last Updated
American College of Rheumatology (ACR)	Practice guidelines for the treatment of osteoarthritis (hand, hip, and knee)	USA	2012
American Geriatrics Society (AGS)	Practice guideline for pharmacologic management of chronic pain	USA	2009
National Institute for Health and Care Excellence (NICE)	Guidance on the management of chronic pain	UK	2013
American Geriatrics Society Beers Criteria for Potentially Inappropriate Prescribing in Older Adults	Evidence-based consensus guidelines on potentially inappropriate medication use in older adults,	USA	2015

Resource	Content	Origin	Last Updated
	including analgesics		
Osteoarthritis Research Society International (OARSI) Guidelines	Guidelines for the management of hip and knee osteoarthritis	Global	2014 (knee); 2010 (hip and knee)

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KEY POINTS

- Pharmacologic management for chronic pain is one part of the multimodal, interdisciplinary approach to the treatment of chronic pain in older adults.
- Topical agents are ideal for an older adult with localized pain that is uncontrolled with other medications (or if specific classes of medications are contraindicated).
- Use of the lowest effective dose of all pharmacologic agents, and consideration of low-dose combination therapy, are especially appropriate in older adults with chronic pain.
- Engage the older adult in determining patient-centered treatment goals and expectations of pain management.
- Establish a careful surveillance plan to determine whether treatment goals are being met and for monitoring potential toxicity of pharmacotherapies for chronic pain.

Table 1

Topical agents

Medication	Indication	Preparation Strength	Formulations	Clinical Pearls
Menthol and menthol salicylate (BenGay, Icy Hot, Salonpas Arthritis Pain)	Generalized pain, minor aches and pain of muscle and joints (arthritis, backache, sprains, strains)	Methyl salicylate 10% Menthol 1.5%–3%	Cream, foam, patch	• Do not leave patch on for >8 h (max 2 patches/24 h) • Avoid applying to wounds or damaged skin • Avoid concurrent use with other topical agents
Capsaicin (Zostrix, Salonpas Gel patch, Qutenza)	Generalized pain, osteoarthritis, postherpetic neuralgia, diabetic neuropathy, HIV neuropathy (off-label use)	0.025%–8%	Cream, gel, lotion, patch	• Several products available over the counter • Caution burns at application site, recommend applying with gloves • High-dose patch (Qutenza) may cause transient increases in blood pressure (monitor)
Lidocaine (Lidoderm, Xylocaine)	Generalized pain, postherpetic neuralgia, topical anesthesia	2%–5%	Cream, gel, jelly, lotion, ointment, oral solution, patch	Use lowest amount necessary for pain relief; a large amount of these products applied for prolonged periods of time increases systemic absorption potentially leading to increased central nervous system and cardiac effects
Diclofenac (Solaraze, Flector, Pennsaid, Voltaren)	Generalized pain, Osteoarthritis (evaluated for hand and knee osteoarthritis)	1%–3%	Cream, gel, solution, patch	• Limited data in older adults with baseline renal insufficiency and taking anticoagulants; monitor carefully • Apply per physician or drug package insert instructions

Abbreviation: HIV, human immunodeficiency virus.

Table 2

Acetaminophen

Medication	Indication	Dosage Range	Clinical Pearls
Acetaminophen (APAP; Tylenol)	Mild-to-moderate pain	Starting dose for older adults is same as for younger adults Consider dose reduction in older adults with risk factors for acetaminophen-related toxicities, for example, frailty, alcohol use (≥3 drinks per day), existing liver insufficiency 325-500 mg every 4 h or 500-1000 mg every 6 h Maximum daily dose: per McNeil Consumer Healthcare, 3000 mg/d; Health care professionals may still prescribe 4000 mg/d and are advised to use their own discretion and clinical judgment	• Consider all sources of acetaminophen (prescription and over the counter) and all routes of administration • Monitoring: check liver function, signs and symptoms of liver injury

Table 3

NSAIDs

Medication	Indication	Dosage Range	Clinical Pearls
Ibuprofen (Motrin)	Mild-to-moderate pain	Consider reduced initial dosage in frailty Renally adjust doses 200 mg 3–4 times per day; maximum daily dose of 3200 mg; administer after meal; if longer term use (eg, >1 mo), GI protection recommended	• Inexpensive • Side effects may be limited by using the lowest effective recommended dose for the shortest time possible
Celecoxib (Celebrex)	Mild-to-moderate pain	100–200 mg/d	• More expensive than other NSAIDs • Higher doses associated with higher incidence of GI and CV side effects; patients with indications for cardioprotection require aspirin • Side effects may be limited by using the lowest effective recommended dose for the shortest time possible
Salsalate (Disalcid)	Mild-to-moderate pain	500–750 mg every 12 h; maximum daily dose of 3000 mg	• Does not interfere with platelet function; GI bleeding and nephrotoxicity are rare • Side effects may be limited by using the lowest effective recommended dose for the shortest time possible

Abbreviations: CV, cardiovascular; GI, gastrointestinal; NSAIDs, nonsteroidal anti-inflammatory drugs.

Table 4

Adjuvant therapies

Medication	Indication	Dosage Range	Clinical Pearls
Antidepressants			
Amitriptyline (Elavil)	Diabetic peripheral neuropathy (off-label)	Start 10 mg/d Titrate at tolerated, lower doses are recommended	Caution anticholinergic effects/burden
Nortriptyline (Pamelor)	Diabetic peripheral neuropathy (off-label) Postherpetic neuralgia (off-label)	Start 10–20 mg/d (bedtime) Titrate every 3–5 d as tolerated in 10 mg increments Max 160 mg/d	• Fewer anticholinergic effects than other tricyclic antidepressants • Preferred in older adult population; however, still need to monitor for anticholinergic effects/ burden
Venlafaxine ER (Effexor XR)	Diabetic peripheral neuropathy (off-label)	Start 37.5 mg/d Titrate to 75–225 mg/d	• Monitor blood pressure, and for increased anxiety or insomnia • May impair platelet aggregation, monitor for bruising and bleeding • Associated with hyponatremia, monitor sodium levels upon initiation, dose changes and periodically during therapy
Duloxetine (Cymbalta)	Diabetic peripheral neuropathy Fibromyalgia	Start 30–60 mg/d Titrate to 60–120 mg/d	• Preferred SNRI for older adults • Well tolerated with reduced incidence of SNRI typical side effects • Association with hyponatremia remains the same as other SNRIs
Anticonvulsants			
Carbamazepine (Tegretol)	Trigeminal neuralgia	Start 200 mg/d BID Titrate to 400–800 mg/d BID	• Several drug interactions • Nausea, edema, insomnia, agitation, Stevens-Johnson syndrome
Oxcarbazepine (Trileptal)	Trigeminal neuralgia (off-label use)	Start 300–600 mg/d BID Titrate to 1500–1800 mg/d BID	Elevated blood pressure, dizziness, drowsiness, headache, agitation, nausea, constipation, vomiting
Lamotrigine (Lamictal)	Trigeminal neuralgia	Start 5 mg/d Titrate to 200–600 mg/d	Monitor for hypersensitivity reactions, (rash, acute urticarial, and extensive pruritus); risk is higher with the coadministration of valproic acid
Gabapentin (Neurontin)	Postherpetic neuralgia Diabetic peripheral neuropathy (off-label) Fibromyalgia (off-label)	Start 300 mg/d TID Titrate to 1800–3600 mg/d TID	• Monitor renal function as gabapentin should be dose adjusted when CrCl <60 mL/min • Caution increased risk for falls due to dizziness and somnolence
Pregabalin (Lyrica)	Postherpetic neuralgia Diabetic peripheral	Start 150 mg/d BID-TID Titrate to 150–300 mg/d BID–TID	• Controlled substance C-IV • Monitor renal function as gabapentin should be dose adjusted when CrCl <60 mL/min

Medication	Indication	Dosage Range	Clinical Pearls
	neuropathy Fibromyalgia		• Caution increased risk for falls due to dizziness and somnolence

Abbreviations: BID, twice a day; CrCl, creatinine clearance; SNRI, serotonin-norepinephrine reup-take inhibitors; TID, 3 times a day.

Table 5

Muscle relaxants

Medication	Indication	Dosage Range	Clinical Pearls
Antispasticity Agents			
Baclofen (Lioresal)	Spasticity	5 mg 2–3 times/d for Max 80 mg/d	• Black box warning: Caution abrupt discontinuation, risk of withdrawal • No dose adjustments required for renal or hepatic dysfunction
Dantrolene (Dantrium)	Spasticity	Start 25 mg (25–100 mg) 4 times a day	• Black bock warning: risk for hepatotoxicity with chronic use, monitor hepatic function • May cause sun sensitivity
Tizanidine (Zanaflex)	Spasticity	Initial 2 mg ≤3 times/d Titrate in 2-4 mg increments per dose over 1–4 d Max 36 mg/d (single doses of >16 mg have not been studied)	• Avoid rapid discontinuation: gradually taper by 2-4 mg/d • Use with caution in older adults who have decreased clearance • Monitor liver function • Monitor QT interval with chronic use
Antispasmodic agents			
Carisoprodol (Soma)	Acute musculoskeletal pain	250–350 mg 3 times/d	• Controlled substance C-IV has been subject to abuse, dependence, withdrawal, misuse, and diversion • Active metabolites with barbiturate effects increasing somnolence and risk of falls for older adults • Caution orthostatic hypotension • Limit use to 2–3 wk
Cyclobenzaprine (Amrix; Flexeril DSC)	Musculoskeletal pain	IR tablet 5 mg 3 times/d Max 10 mg 3 times/d Extended-release tables – not recommended for geriatric patients	• Caution anticholinergic effects/burden • Not recommended in mild to severe hepatic impairment • Do not use within 14 d of MAOIs
Metaxolone (Skelaxin)	Musculoskeletal pain	800 mg 3–4 times/d	• Absorption is increased when taken with food • Contraindicated in severe hepatic and renal dysfunction, monitor liver function
Methocarbamol (Robaxin)	Musculoskeletal pain	750–1000 mg orally every 4 hours, up to 4 g/day for maintenance Max 4 g/d	• Use lower doses at initiation of drug especially with geriatric patients, titrate as clinically indicated • No dose adjustments required for renal or hepatic dysfunction • Drug may change color of urine to brown, black, or green

Abbreviations: IR, immediate release; MAOI, monoamine oxidase inhibitors.