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Review Article

Pharmacological Management of Persistent Pain in Older Persons

American Geriatrics Society Panel on the Pharmacological Management of Persistent Pain in Older Persons

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Pain is a complex phenomenon caused by noxious sensory stimuli or neuropathological mechanisms. An individual's memories, expectations, and emotions modify the experience of pain [1]. Persistent pain, by definition, continues for a prolonged period of time and may or may not be associated with a well-defined disease process. In the medical literature, the terms "persistent pain" and "chronic pain" are often used interchangeably, but the newer term, "persistent pain," is preferred, because it is not associated with the negative attitudes and stereotypes that clinicians and patients often associate with the "chronic pain" label [2]. In the definition of persistent pain, authors have used various durations of painful sensation, including pain longer than 3 months, 6 months, or more. Some reports make the assumption that patients with certain diagnoses, such as postherpetic neuralgia, low back pain, or cancer-related pain, must also experience persistent pain. In the final analysis, readers must evaluate new additions to the medical literature carefully and consider how these sometimes arbitrary definitions apply to each clinical situation and individual patient.

Demographers, insurers, and employers have defined older persons as aged 65 and older. By age 75, many persons exhibit some frailty and chronic illness, with many having multiple chronic illnesses. In the population aged 75 and older, morbidity, mortality, and social problems increase rapidly, resulting in substantial strains on the healthcare system and social safety net [3,4]. The American Geriatrics Society (AGS) Panel on Pharmacological Management of Persistent Pain in Older Persons focused its attention on this older frail population in preparing this update.

Persistent pain commonly affects older people [5–7] and is most frequently associated with musculoskeletal disorders, such as degenerative spine conditions and arthritis. Night-time leg pain (stemming from muscle cramps, restless legs, or other conditions) and pain from claudication are also common. As many as 80% of older persons diagnosed with cancer experience pain during the course of their illness [8], and pain that occurs as a consequence of cancer treatment is increasingly recognized as a form of persistent pain [9]. The distress of cancer pain creates an obligation for clinicians to provide effective pain management, particularly near the end of life. Persistent pain is also frequently encountered in nursing homes. Many nursing home residents have multiple complaints and numerous potential sources of pain [10,11]. Neuralgia secondary to diseases such as diabetes mellitus, infections such as herpes zoster, peripheral vascular disease, and trauma, including surgery, amputation, and other nerve injuries, is somewhat less frequent.

Persistent pain or its inadequate treatment is associated with a number of adverse outcomes in older people, including functional impairment, falls, slow rehabilitation, mood changes (depression and anxiety), decreased socialization, sleep and appetite disturbance, and greater healthcare use and costs [12]. Although appropriate treatment can reduce these adverse events, the treatments themselves may incur their own risks and morbidities. Persistent pain can also be as distressing for the caregiver as for the patient. Caregiver strain and negative caregiver attitudes can substantially affect the patient's experience of pain and should be evaluated and discussed during the clinical encounter, if present.

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AGS Panel on Pharmacological Management of Persistent Pain in Older Persons.

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Guideline Development Process and Methods

The American Geriatrics Society (AGS) provided the first Clinical Practice Guideline on management of chronic pain in older persons in 1998 [13]. This landmark publication became a call to arms for improving pain management, quality of life, and quality of care for older patients. In 2002, the publication was revised to include new pharmacological and other strategies for improving patient care, as well as new information on the assessment of pain in patients with cognitive impairment [12]. The focus of these efforts has been to provide education and guidance to primary care clinicians, researchers, and other health professionals as they encounter patients with persistent pain and its complications.

The current Guideline aims to update the evidence base of the 2002 Guideline and provide recommendations regarding the use of newer pharmacological approaches to managing persistent pain in the older population. Since the development of the two previous AGS publications, substantial progress has been made in this area. New drugs have been introduced, management strategies have been more fully evaluated, and new treatment approaches are now available. In particular, many recent reports describing novel pharmacological approaches to management warrant an appropriate revision to the 2002 publication at this time.

Because the most common strategy for management of persistent pain in older persons is the use of pharmacological agents, and because this is also the area of greatest risk, it was decided to focus on pharmacotherapy in this update. This document is not an exhaustive treatise; rather, it is offered as a synthesis of existing literature and the consensus of experts familiar with clinical pain management, research in older persons, and the diverse settings in which care is often provided, including ambulatory care settings and nursing homes. As such, it is hoped that this guideline update proves helpful to clinicians, researchers, and policy makers alike. Ultimately, it is hoped that the beneficiaries of this work will be older patients who often require effective pain management to maintain their dignity, functional capacity, and overall quality of life.

The development of this guideline update was begun by convening a panel comprising members from the previous panels and new members with substantial knowledge, experience, and publications in pain management and care of older patients. Panel members included experts in geriatric pain management, pharmacology, rheumatology, neurology, nursing, palliative care, and geriatric clinical practice. Beginning with a review of previous guidelines from the AGS, American Pain Society, American College of Rheumatology, and others, the panel conducted a review of evidence-based literature published since the preceding AGS guidelines appeared and then drafted new recommendations. An independent researcher was commissioned to conduct a literature search. More than 24,000 citations were identified from sources such as computerized key word searches for each recommendation, personal citation libraries of the panel members, and references from texts of some individual articles. Of these, approximately 2,400 abstracts were screened for evidence-based content. Detailed summaries were created along with the full-text articles for more than 240 full-text English-language articles. Data from these articles (formal meta-analyses, randomized controlled trials, other clinical trials) were reviewed to determine the strength and quality of evidence for the recommendations based on a modified version of the Grading of Recommendations Assessment, Development, and Evaluation Working Group [14,15] that the American College of Physicians developed for their Guideline Grading System [16]. Through a consensus process, panel members assigned strength and quality of evidence to each recommendation. Table 1 provides a key to the designations used.

Current evidence-based literature does not serve as an adequate guide in many decision-making situations that are routinely encountered in clinical practice. For example, much existing evidence is focused on disease-specific conditions or on younger populations with limited generalizability. Also, the number of controlled studies involving only patients aged 75 and older remains low. Furthermore, high-quality studies involving elderly patients from different ethnic groups are rare. Therefore, some of the recommendations are based on the clinical experience and the consensus of panel members, as well as the existing weak scientific evidence. When appropriate, the panel drew on studies of younger subjects that could be extrapolated to older individuals, but extrapolation to the oldest old or to care settings where older persons often reside was not always reasonable. Once the literature review was completed, evidence was rated, and the document was disseminated for external review by experts from a variety

Table 1 Key to designations of quality and strength of evidence

Quality of evidence	
High	Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes (≥2 consistent, higher-quality randomized controlled trials or multiple, consistent observational studies with no significant methodological flaws showing large effects).
Moderate	Evidence is sufficient to determine effects on health outcomes, but the number, quality, size, or consistency of included studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes (≥1 higher quality trial with >100 subjects; ≥2 higher-quality trials with some inconsistency; ≥2 consistent, lower-quality trials; or multiple, consistent observational studies with no significant methodological flaws showing at least moderate effects) limits the strength of the evidence.
Low	Evidence is insufficient to assess effects on health outcomes because of limited number or power of studies, large and unexplained inconsistency between higher-quality studies, important flaws in study design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.
Strength of recommendation	
Strong	Benefits clearly outweigh risks and burden OR risks and burden clearly outweigh benefits.
Weak	Benefits finely balanced with risks and burden.
Insufficient	Insufficient evidence to determine net benefits or risks.

of other organizations with interest in this subject. (See Acknowledgments for listing of review organizations.)

Each expert panel member completed a disclosure form at the beginning of the guideline process that was shared with the entire expert panel at the start of its two expert panel meetings. Conflicts of interest in this guideline have been resolved by having the guideline independently peer reviewed and then edited by the Expert Panel Chair, who had no conflict of interest with the medications being discussed. Expert panel members who disclosed affiliations or financial interests with commercial interests involved with the products or services referred to in the guideline are listed under the disclosures section of this article.

Some matters involving pharmacological management of persistent pain in older persons were beyond the scope of this publication. For example, the use of anesthetic agents, chronic infusions, and neurostimulatory and implantable pump technologies were not addressed. It is hoped that this update will stimulate others to focus on solutions to the significant issues not addressed here.

The update begins with a review of pain assessment principles. The recommendations that follow have been grouped under the following headings: nonopioids, including acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs); opioid analgesics; adjuvant drugs; and other medications. General principles are discussed first, followed by the panel's specific recommendations for use of these medications. Readers should recognize that medical science is constantly evolving and that clinicians have a responsibility to keep abreast of new developments. New and emerging evidence may have important implications for the implementation of specific recommendations contained in this document. These recommendations are intended as a guide. They should not substitute for critical thinking, sound judgment, clinical experience, and an open-minded approach to the unique individual circumstances of each clinical encounter.

Assessment and Management of Persistent Pain

General Principles

The approach to pain management in older persons differs from that for younger people. Clinical manifestations of persistent pain are often complex and multifactorial in the older population. In addition, older people may underreport pain. Concurrent illnesses and multiple problems make pain evaluation and treatment more difficult. Also, older persons are more likely to experience medication-related side effects and have a higher potential for complications and adverse events related to diagnostic and invasive procedures. Despite these challenges, pain can usually be effectively managed in this age group. Moreover, clinicians have an ethical and moral obligation to prevent needless suffering and do their best to provide effective pain relief, especially for those near the end of life.

An effective pharmacological approach to the treatment of persistent pain requires accurate pain assessment. Routine screening and careful assessment of all older patients is crucial, because even pain that is causing severe impairment may not be spontaneously revealed for a variety of personal, cultural, or psychological reasons [12]. Not only do many older persons underreport pain, but there are also inherent difficulties in recognizing pain experienced by patients with cognitive impairment. A thorough initial assessment and appropriate diagnostic evaluation are always necessary and

may reveal disease-modifying interventions that can potentially relieve pain at the source [17]. Interdisciplinary assessment during the evaluation process may help identify all such treatable contributing factors. For patients whose underlying pain source is not remediable or only partially treatable, an interdisciplinary assessment and treatment strategy is the best approach [18,19]. When specialized services or skilled procedures are indicated, referral to an appropriate specialist is necessary. For example, patients with debilitating psychiatric complications, problems of substance abuse, or life-altering intractable pain require referral to specialists with relevant expertise [12].

The current best indicator of the pain experience is the patient's own report, which must include an assessment of the pain intensity and an evaluation of the effect of the pain on daily function [20]. Even in the presence of mild or moderate cognitive impairment, an assessment can be made using simple questions and screening tools, including a variety of pain scales that have been developed specifically for this purpose [21–25]. Approaches for recognizing and evaluating pain in nonverbal older persons are also available [26]. Readers are referred to a recent systematic review for details of the current state of the art in assessment of pain in older persons [27] and to previous AGS guidelines (http://www.americangeriatrics.org) for specific recommendations for pain assessment in older persons that remain relevant [12,13].

General Principles of Pharmacological Management

Any pain complaint that affects physical function or quality of life should be recognized as a significant problem. Older patients with functional impairment or diminished quality of life are candidates for pharmacological therapy, with intervention decisions based on careful weighing of risks and benefits. Positive outcomes are maximized when clinicians are knowledgeable about the drugs they prescribe and regularly monitor patients for adverse effects, although it is unrealistic to imply, or for patients to expect, complete absence of pain for some persistent pain conditions [12]. Comfort goals should be mutually established for managing pain to a level that allows the patient to engage in activities and achieve an acceptable quality of life.

Although older patients are generally at higher risk of adverse drug reactions, analgesic and pain-modulating drugs can still be safe and effective when comorbidities and other risk factors are carefully considered. It must be assumed that there will be age-associated differences in effectiveness, sensitivity, and toxicity and that pharmacokinetic and pharmacodynamic drug properties will change in this population [28–31]. Table 2 provides a summary of changes observed with normal aging

Table 2 Pharmacological changes with aging

Pharmacological Concern	Change with Normal Aging	Common Disease Effects
Gastrointestinal absorption or function	• Slowing of gastrointestinal transit time may prolong effects of continuous-release enteral drugs. • Opioid-related bowel dysmotility may be enhanced in older patients.	• Disorders that alter gastric pH may reduce absorption of some drugs. • Surgically altered anatomy may reduce absorption of some drugs.
Transdermal absorption	• Under most circumstances, there are few changes in absorption based on age but may relate more to different patch technology used.	• Temperature and other specific patch technology characteristics may affect absorption.
Distribution	• Increased fat to lean body weight ratio may increase volume of distribution for fat-soluble drugs.	• Aging and obesity may result in longer effective drug half-life
Liver metabolism	• Oxidation is variable and may decrease resulting in prolonged drug half-life. • Conjugation usually preserved. • First-pass effect usually unchanged. • Genetic enzyme polymorphisms may affect some cytochrome enzymes.	• Cirrhosis, hepatitis, tumors may disrupt oxidation but not usually conjugation.
Renal excretion	• Glomerular filtration rate decreases with advancing age in many patients, which results in decreased excretion.	• Chronic kidney disease may predispose further to renal toxicity.
Active metabolites	• Reduced renal clearance will prolong effects of metabolites.	• Renal disease. • Increase in half-life.
Anticholinergic side effects	• Increased confusion, constipation, incontinence, movement disorders.	• Enhanced by neurological disease processes.

that can affect disposition, metabolism, and responses to analgesic medications.

For some classes of pain-relieving medications (e.g., opioids), older patients have demonstrated greater analgesic sensitivity, but older people constitute a heterogeneous population, making optimum dosage and common side effects difficult to predict. Recommendations for age-adjusted dosing are not available for most analgesics. In reality, dosing for most patients requires initiation with low doses followed by careful upward titration, including frequent reassessment for dosage adjustments and optimum pain relief and for adverse effects.

The least-invasive method of drug administration should be used. Some opioids, for example, can be administered through a variety of routes, including oral, subcutaneous, intravenous, transdermal, oral sublingual, intrathecal, and rectal. Most drugs are limited to only a few safe routes of administration, but new delivery systems are being developed each year. As a rule, the oral route is preferable because of its convenience and the relatively steady blood concentrations that result. Some drug effects are seen in 30 minutes to 2 hours after oral administration of analgesics; this may be inadequate for acute, rapidly fluctuating pain. Intravenous bolus provides the most rapid onset and shortest duration of action but requires more labor, technical skill, and monitoring than oral administration. Although commonly used, subcutaneous and intramuscular injections have disadvantages such as wider fluctuations in absorption and more rapid fall-off of action than the oral route. Transdermal, rectal, and oral transmucosal routes may be essential for people with swallowing difficulties.

Timing of medication administration is also important. Rapid-onset, short-acting analgesic drugs should be used for severe episodic pain. Medications for intermittent or episodic pain can usually be prescribed as needed, although the as-needed approach is not a good choice for patients with cognitive impairment who are not able to request medication appropriately. Scheduled administration before anticipated (or incident) pain episodes is recommended in these patients. For continuous pain, medications should be provided around the clock. In these situations, a steadystate analgesic blood concentration maintains comfort more effectively. Most patients with continuous pain who are receiving long-acting or sustained-release preparations should also have fast-onset short-acting drugs for break-through pain. Breakthrough pain includes end-of-dose failure, resulting from decreased blood concentrations of analgesic with concomitant increase in pain before the next scheduled dose; incident pain, usually caused by activity that can be anticipated and pretreated; and spontaneous pain, common with neuropathic pain that is often fleeting and difficult to predict.

The use of placebos is unethical in clinical practice and in the management of pain. Inert oral placebo medications, sham injections, or other fraudulent procedures are used in some analgesic studies, but patient consent and full understanding must be ensured in such cases. In clinical settings, placebo effects are common, but they are not diagnostic of pain or indicative of a therapeutic response. Not only are the effects of placebos often short lived, but most importantly, deceptive placebo administration may lead to loss of patient trust in addition to needless suffering.

For many patients, combining pharmacological and nonpharmacological strategies (including complementary or alternative medicine) can enhance relief of persistent pain. Although some nonpharmacological interventions have been shown to reduce pain when used alone, their benefit is usually enhanced when combined with drug strategies. Effective nonpharmacological approaches include physical therapy, cognitive behavioral therapy, and most importantly, patient and caregiver education interventions. Readers are referred to the 2002 AGS guidelines and recent reviews for a more-detailed description [12,32,33].

More than a single drug may be necessary to attain a specific therapeutic endpoint. Moreover, a combination of two or more drugs with complementary mechanisms of action may work synergistically to afford greater relief with less toxicity than would higher doses of a single agent. This strategy, which has become known as "rational polypharmacy," may be particularly important for some patients or conditions in which no single agent can produce pain relief without dose-limiting adverse effects.

Pharmacotherapy

Nonopioid Analgesics

Table 3 summarizes the recommended drugs for treatment of persistent pain in older adults. Acetaminophen is an effective agent for the management of symptoms of osteoarthritis and low back pain [34,35]. It is not associated with

Table 3 Recommended drugs for persistent pain in older adults

Drug	Recommended Starting Dose*	Comments
Nonopioid analgesic		
Acetaminophen (Tylenol)	325–500 mg every 4 h or 500–1,000 mg every 6 h	Maximum dose usually 4 g daily. Reduce maximum dose 50% to 75% in patients with hepatic insufficiency or history of alcohol abuse.
Choline magnesium trisalicylate (Tricosal, Trilisate)	500–750 mg every 8 h	Long half-life may allow daily or twice-daily dosing after steady state is reached. Minimal antiplatelet effect.
Salsalate (e.g., Disalcid, Mono-Gesic, Salflex)	500–750 mg every 12 h	In frail patients or those with diminished hepatic or renal function, it may be important to check salicylate levels during dose titration and after reaching steady state. Minimal antiplatelet effect.
Celecoxib (Celebrex)	100 mg daily	Higher doses associated with higher incidence of gastrointestinal, cardiovascular side effects. Patients with indications for cardioprotection require aspirin supplement; therefore, older individuals will still require concurrent gastroprotection.
Naproxen sodium	220 mg twice daily	Several studies implicate this agent as possessing less cardiovascular toxicity.
Ibuprofen	200 mg three times a day	Food and Drug Administration indicates concurrent use with aspirin inhibits aspirin's antiplatelet effect, but the true clinical import of this remains to be elucidated, and it remains unclear whether this is unique to ibuprofen or true with other NSAIDs.
Diclofenac sodium	50 mg twice daily or 75 mg extended release daily	Owing to its relative cyclooxygenase-2 inhibitor selectivity, this agent may be associated with higher cardiovascular risk compared to other traditional NSAIDs.
Nabumetone (Relafen)	1 g daily	Relatively long half-life and minimal antiplatelet effect associated with this agent (>5 days).
Ketorolac		Not recommended. High potential for adverse gastrointestinal and renal toxicity; inappropriate for long-term use.
Opioid		
Hydrocodone† (Lorcet, Lortab, Norco, Vicodin, Vicoprofen)	2.5–5 mg every 4–6 h	Useful for acute recurrent, episodic, or breakthrough pain; daily dose limited by fixed-dose combinations with acetaminophen or NSAIDs. Prescribers need to consider the amount of nonopioid agent in each of these preparations—they are not all the same—and other acetaminophen or NSAID-containing preparations the patient is taking, including over-the-counter medications.
Oxycodone‡ (OxyIR, Percocet, Percodan, Tylox, Combunox)	2.5–5 mg every 4–6 h	Useful for acute recurrent, episodic, or breakthrough pain; daily immediate-release dose limited by fixed-dose combinations with acetaminophen or NSAIDs. Immediate-release oxycodone is available without added co-analgesics. Prescribers should specify which oxycodone preparation they want for their patient to avoid confusion or co-analgesic toxicity.
(OxyContin)	10 mg every 12 h	Usually started after initial dose determined by effects of immediate-release opioid or as an alternative to a different long-acting opioid because of indications for opioid rotation. Although intended for 12-hour dosing, some patients only get 8 hours of effective analgesia, whereas some frail older patients get 12 to 24 hours of relief.
Morphine		
Immediate release (MSIR, Roxanol)	2.5–10 mg every 4 h	Available in tablet form and as concentrated oral solution, which is most commonly used for episodic or breakthrough pain and for patients unable to swallow tablets.
Sustained release (Avinza, Kadian, MSContin, Oramorph SR)	15 mg every 8–24 h (see dosing guidelines in the package insert for each specific formulation)	Usually started after initial dose determined by effects of immediate-release opioid or as an alternative to a different long-acting opioid due to indications for opioid rotation. Toxic metabolites of morphine may limit usefulness in patients with renal insufficiency or when high-dose therapy is required. Continuous-release formulations may require more-frequent dosing if end-of-dose failure occurs regularly. Significant interactions with food and alcohol toxicity.
Hydromorphone (Dilaudid, Hydrostat)	1–2 mg every 3–4 h	For breakthrough pain or for around-the-clock dosing.

Table 3 Continued

Drug	Recommended Starting Dose*	Comments
Methadone (Dolophine)		Use recommended only by practitioners knowledgeable in its pharmacology and experienced in its use. Highly variable half-life and nonlinear dose equivalencies when switching from other opioids. Not recommended as first-line agent.
Oxymorphone		
Immediate release (Opana IR)	5 mg every 6 h	Typical opioid side effects. Significant interactions with food and alcohol toxicity.
Extended release (Opana ER)	5 mg every 12 h	Usually started after initial dose determined by effects of immediate-release opioid or as an alternative to a different long-acting opioid because of indications for opioid rotation.
Transdermal fentanyl (Duragesic)	12–25 mcg/h patch every 72 h	Started after initial dose determined by effects of immediate-release opioid or as an alternative to a different long-acting opioid because of indications for opioid rotation. Currently available lowest-dose patch recommended for patients who require <60 mg per 24-hour oral morphine equivalents. Peak effects of first dose takes 18 to 24 hours. Duration of effect is usually 3 days but may range from 48 hours to 96 hours. May take two to three patch changes before steady-state blood levels reached.
Adjuvant drug		
Tricyclic Antidepressant*		
Desipramine (Norpramine), Nortriptyline (Aventyl, Pamelor), Amitriptyline (Elavil)	10 mg at bedtime	Significant risk of adverse effects in older patients. Anticholinergic effects (visual, urinary, gastrointestinal); cardiovascular effects (orthostasis, atrioventricular blockade). Older persons rarely tolerate doses greater than 75 to 100 mg per day.
Other Antidepressant*		
Duloxetine (Cymbalta)	20 mg daily	Monitor blood pressure, dizziness, cognitive effects and memory. Has multiple drug–drug interactions.
Venlafaxine (Effexor)	37.5 mg daily	Venlafaxine associated with dose-related increases in blood pressure and heart rate.
Milnacipran (Savella)	50 mg twice daily/starting dose 12.5 mg once a day See package insert for titration recommendations. Discontinuation requires tapering.	Caution in renal insufficiency with creatinine clearance less than 30 mL/min, reduce dose by 50%. Common reactions include nausea, constipation, hot flashes, hyperhidrosis, palpitations, dry mouth, hypertension. Contraindicated with monoamine oxidase inhibitors and narrow-angle glaucoma.
Anticonvulsant		
Carbamazepine (Tegretol)	100 mg daily	Monitor hepatic transaminases (aspartate transaminase, alanine transaminase), complete blood count, creatinine, blood urea nitrogen, electrolytes, serum carbamazepine levels. Multiple drug–drug interactions.
Gabapentin (Neurontin)	100 mg at bedtime	Monitor sedation, ataxia, edema.
Pregabalin (Lyrica)	50 mg at bedtime	Monitor sedation, ataxia, edema.
Lamotrigine (Lamictal)	25 mg at bedtime	Monitor sedation, ataxia, cognition. Associated with rare cases of Stevens-Johnson syndrome.
Antiarrhythmic		
Mexiletine (Mexitil)	150 mg twice daily	Monitor electrocardiogram at baseline and after dose stabilization. Avoid use in patients with conduction block, bradyarrhythmia.
Other drugs		
Corticosteroids (prednisone, methylprednisolone) (e.g., Deltasone, Medrol dose pak Liquid Pred, Orasone)	Example: 5 mg prednisone daily and taper as soon as feasible	Use lowest possible dose to prevent steroid effects. Anticipate fluid retention and glycemic effects in short-term use and cardiovascular and bone demineralization with long-term use.
Lidocaine (topical) (Lidoderm 5%)	1–3 patches for 12 hours per day	Monitor for rash or skin irritation.

Table 3 Continued

Drug	Recommended Starting Dose*	Comments
Muscle Relaxant		
Baclofen (Lioresal)	5 mg up to three times daily	Monitor muscle weakness, urinary function, cognitive effects, sedation. Avoid abrupt discontinuation because of central nervous system irritability. Older persons rarely tolerate doses greater than 30 to 40 mg per day.
Tizanidine (Zanaflex)	2 mg up to three times daily	Monitor muscle weakness, urinary function, cognitive effects, sedation, orthostasis. Potential for many drug–drug interactions.
Clonazepam (Klonopin)	0.25–0.5 mg at bedtime	Monitor sedation, memory, complete blood count.
Cannabinoid		
Nabilone (Cesamet)	1 mg daily or twice daily	Monitor ataxia, cognitive effects, sedation. High incidence of dizziness or drowsiness. Cardiovascular effects with tetrahydrocannabinol or cannabidiol. Older persons may be prone to postural hypotension. Nabilone is approved for nausea and vomiting but may help with some pain syndromes.
Dronabinol (Marinol)	2.5 mg once or twice daily	Dizziness, somnolence, cognitive impairment, dysphoria.
Dual-mechanism Drug		
Tramadol (Ultram/Ultram ER)	12.5–25 mg every 4–6 h	Mixed opioid and norepinephrine or serotonin reuptake inhibitor mechanisms of action. Monitor for opioid side effects, including drowsiness, constipation and nausea. Risk of seizures if used in high doses or in predisposed patients. May precipitate serotonin syndrome if used with selective serotonin reuptake inhibitors.
Tapentadol (Nucynta)	50 mg every 4–6 h by mouth (equivalent to oxycodone 10 mg every 4–6 hr by mouth)	Clinical trials of tapentadol suggest lower incidence of gastrointestinal adverse events than comparator opioids.

This table is meant to highlight common agents for the purposes of illustrating potentially underappreciated features of particular drugs. This table is not an endorsement of any therapeutic agent, nor is it intended to reflect a hierarchy of treatment. Similarly it is not meant to be an exhaustive listing. Doses listed should be checked with manufacturer's recommendations.

* Lowest starting dose should be considered in frail older persons with a history of sensitivity to central nervous system–active drugs.

† Only available in combination with acetaminophen or nonsteroidal anti-inflammatory drug (NSAID); see guideline for dose limitations based upon co-analgesic.

‡ Available with or without acetaminophen or NSAID: see guideline for dose limitations based upon co-analgesic.

significant gastrointestinal bleeding, adverse renal effects, or cardiovascular toxicity, although some evidence of longterm renal toxicity has been reported if acetaminophen is used in high doses over many years [36,37]. Owing to its greater safety than traditional NSAIDs, acetaminophen is recommended as first-line therapy for pain [38]. Clinicians should carefully address how much or how little acetaminophen the patient is taking before making a decision about a stronger pain medication. Sometimes an increase of acetaminophen dose to 1,000 mg provides a pain relief effect so that stronger medications are not required. Clinicians should also educate patients on the maximum safe dose (<4 g/24 hours) of acetaminophen from all sources.

Older individuals often suffer from persistent musculoskeletal pain that is commonly treated with acetaminophen or NSAIDs. Although concern about hepatic toxicity with acetaminophen has been raised, it appears that the transient elevations of alanine aminotransferase that have been observed in long-term patients do not translate into liver failure or hepatic dysfunction when maximum recommended doses are avoided [39,40].

Acetaminophen is less effective for chronic inflammatory pain (such as the pain associated with rheumatoid arthritis) than NSAIDs [41]. Another potential advantage of NSAIDs over acetaminophen may be better short-term (e.g., 6 weeks) effectiveness for relieving osteoarthritis pain [42,43]. NSAIDs relieve short-term low back pain as well [44,45]. In the general adult population, over-the-counter dosing of selected NSAIDs has a good safety profile [46], although older adults are at higher risk for adverse NSAID effects. Particular caution must be exercised when considering NSAID therapy for individuals with low creatinine clearance, gastropathy, cardiovascular

disease, or intravascularly depleted states such as congestive heart failure. A recent study of adverse drug reactions as a cause of hospitalization in older adults (≥65) implicated NSAIDs in 23.5% of cases [47]. This alone dictates particular caution with the use of all such agents.

In older persons, NSAID-associated adverse events include significant gastrointestinal toxicity [48], which increases in frequency and severity with age [49]. At least in part, the gastrointestinal toxicity of NSAIDs may be dose related and time dependent [50,51]. Some small studies have found that nonacetylated NSAIDs (e.g., salsalate) possess lower gastrointestinal toxicity than aspirin [52,53], although therapy with salsalate does not guarantee that gastrointestinal damage will not occur [54]. The concern for gastrointestinal bleeding in chronic NSAID users is heightened in the setting of co-administration with low-dose aspirin, often employed for cardioprotective purposes [55,56].

Cyclooxygenase-2 (COX-2) selective inhibitor NSAIDs were introduced in the hopes of mitigating traditional NSAID-related adverse effects [57]. For example, celecoxib appears to have fewer significant gastrointestinal adverse events associated with its use, whereas it maintains comparable clinical efficacy with traditional NSAIDs [58–60]. However, the protection afforded by COX-2 selective inhibition against gastrointestinal bleeding is not complete, and other NSAID-related toxicities are no different with COX-2 inhibitors [61]. The COX-2 selective inhibitors rofecoxib and valdecoxib were withdrawn from the market because of the associated risk of adverse cardiovascular events [62].

Topical NSAIDs such as diclofenac or salicylate derivatives have been used in hopes of averting systemic NSAID-related adverse effects [63]. These agents appear to be safe and potentially effective over the short term (e.g., <4 weeks in many studies) [64,65]. Adequate long-term studies are currently not available.

A third strategy to address potential NSAID toxicity involves co-administration of gastroprotective agents [66]. Concomitant administration of misoprostol, high-dose H_2-receptor antagonists, or proton pump inhibitors may reduce the risk for gastrointestinal ulceration in chronic NSAID users [67]. Whether an NSAID prescribed along with a proton pump inhibitor or monotherapy with a COX-2 selective inhibitor provides superior protection from incident dyspepsia, bleeding, or other gastrointestinal tract complications remains unclear [68,69]. In individuals at high risk for recurrent gastrointestinal bleeding or ulceration, some evidence highlights the benefits of co-administration of a proton pump inhibitor with a COX-2 inhibitor [70,71].

Finally, eradication of *Helicobacter pylori* reduces the incidence of peptic ulceration in the population exposed to NSAIDs [72–75].

Special Considerations in the Use of Nonopioid Analgesics

Traditional and selective NSAIDs may adversely affect blood pressure control [76–78], renal function [79,80], and heart-failure management [81]. Some traditional NSAIDs also have the in vitro capacity to interfere with the antiplatelet effect of aspirin therapy [82]. To this end, the Food and Drug Administration (FDA) issued a warning in 2006 concerning the co-administration of aspirin and ibuprofen. The cardiovascular risks associated with NSAIDs (traditional and selective) deserve special attention [83,84]. For example, a greater risk of myocardial infarction has been described in COX-2 inhibitor users [85–87]. Of the traditional NSAIDs, diclofenac has been identified as possessing potentially higher risk for adverse cardiovascular events [88,89]. Although earlier recommendations suggested a trial of NSAIDs if acetaminophen is ineffective, newer information suggests that this is often a risky strategy in older adults. The decision to prescribe NSAIDs in the management of persistent pain in older adults demands individualized consideration. Comorbidities, concomitant medications, and associated risk factors (including, possibly, genetics) all affect the decision to introduce such treatment. In some individuals, particularly those with previous positive experience with use of NSAIDs, decision-making must weigh the potential benefits of the improved function and health status that NSAIDs may provide against the risk profile. Key issues in the selection of NSAID therapy are pain amelioration, cardiovascular risk, nephrotoxicity, drug interactions, and gastrointestinal toxicity. In individuals in whom NSAID therapy is considered and in whom gastrointestinal risk is considered low, it may be reasonable to recommend or prescribe ibuprofen or naproxen. If gastrointestinal risk is higher, many physicians co-prescribe a proton pump inhibitor. In addition, if gastrointestinal risk is higher but not cardiovascular risk, and a COX-2 inhibitor is chosen, some clinicians recommend co-administration of a low-dose aspirin to provide cardioprotection. Finally, if higher gastrointestinal

risk is present along with significant cardiovascular concern, low-dose aspirin with naproxen or a COX-2 inhibitor may be a more-reasonable therapeutic compromise than narcotics or other drugs.

Opioid Analgesics

In properly selected and monitored patients, opioid analgesics constitute a potentially effective and, for some patients, indispensable treatment as part of a multimodal strategy in the management of various types of persistent cancer and noncancer pain [90–95]. Clinical observations and the evidence provided by numerous published clinical trials have led to the development of clinical guidelines regarding the use of opioids in patients with persistent noncancer pain by the American Pain Society, American Academy of Pain Medicine, AGS, and others [12,96,97]. Furthermore, the evidence that use of NSAIDs and COX-2 inhibitors may result in serious and life-threatening gastrointestinal and cardiovascular adverse events or gastrointestinal bleeding has shifted attention to opioids, especially for older patients who may be at particular risk for NSAID-related adverse effects [84]. Controlled trials have established the efficacy of various opioids in the treatment of persistent pain associated with musculoskeletal conditions, including osteoarthritis [98] and low back pain [99,100], and in the management of several neuropathic pain conditions, such as diabetic peripheral neuropathy and postherpetic neuralgia [101]. Nonetheless, evidence of long-term effectiveness for persistent noncancer pain conditions in all age groups is lacking. Two recent meta-analyses [102,103] and a number of systematic reviews [104–106] highlight the difficulties of assessing clinical trial data in support of opioid therapy for long-term management of persistent pain. The proper positioning of opioid therapy for older patients with persistent noncancer pain is based on comparing the potential efficacy and risks with those of other modalities and balancing them against the harms of unrelieved pain and potential adverse effects of opioid therapy.

All practitioners who care for older patients—geriatricians, pain specialists, and primary care providers—must consider their own clinical experience along with published evidence when deciding whether and how they will prescribe opioids. Use of opioids in older patients with persistent pain should be prescribed on a trial basis with clearly defined therapeutic goals. The trial may involve serial attempts to titrate the opioid to an efficacious dose without intolerable adverse effects. It should be understood that opioids will be discontinued if the trial is unsuccessful. In most persistent pain conditions that warrant opioid therapy, optimum management requires a comprehensive treatment program that also involves functional restorative and psychosocial modalities. Patients and their caregivers must understand that opioids are not a panacea or substitute for nonpharmacological therapies. On this basis, a trial of opioid therapy for older patients with moderate to severe persistent pain should be considered, guided by the following two sets of questions [107].

(I) Initial Evaluation
  (1) What is conventional practice for this type of pain or patient?
  (2) Is there an alternative therapy that is likely to have an equivalent or better therapeutic index for pain control, functional restoration, and improvement in quality of life?
  (3) Does the patient have medical problems that may increase the risk of opioid-related adverse effects?
  (4) Is the patient likely to manage the opioid therapy responsibly (or relevant caregiver likely to responsibly comanage)?

(II) Role of Consultant or Specialist
  (1) Am I able to treat this patient without help?
  (2) Do I need the help of a pain specialist or other consultant to co-manage this patient?
  (3) Are there appropriate specialists and resources available to help me co-manage this patient?
  (4) Are the patient's medical, behavioral or social circumstances so complex as to warrant referral to a pain medicine specialist for treatment?

Risks and Benefits of Long-Term Opioid Therapy

The potential adverse effects associated with opioids can present a barrier to long-term treatment. Although most of the adverse effects decrease with long-term use (with the notable exception of constipation), adverse events can be sufficiently debilitating to cause patients to discontinue therapy [103,108]. Respiratory depression, which affects respiratory rate, minute volume, and oxygen saturation, is the most serious adverse event and therefore deserves special consideration,

although tolerance to this effect develops quickly. With long-term opioid therapy, respiratory depression usually results from excessively rapid dosing increases, drug–drug interactions with other central nervous system depressants (most notably benzodiazepines, alcohol, and barbiturates), and drug accumulation or accidental overdose from opioids with variable pharmacokinetic profiles, such as methadone [109,110]. Recent evidence has also shown that long-term opioid therapy may suppress the production of several hypothalamic, pituitary, gonadal, and adrenal hormones, manifesting most commonly as testosterone deficiency in men, with associated fatigue, depression, and decreased libido [111].

When used over a protracted period of time, prescription opioid abuse may become a concern, especially in patients with a prior history of a substance use disorder (including tobacco use) [112,113]. Prescription opioid diversion and use of these agents outside specified medical indications and directions has placed an increasingly significant burden on the healthcare system and on society as a whole. Associated financial costs, including medical costs, lost productivity, and the additional burden on the criminal justice system, reached an estimated $9.5 billion in the United States in 2005 [114].

Addiction is a chronic, neurobiological disease characterized by one or more of the following behaviors: impaired control over drug use, compulsive use, continued use despite harm, and craving [115]. The likelihood that a patient will abuse opioid medications correlates with a number of genetic and environmental factors [116], and for those who are genetically predisposed, certain factors will precipitate the addiction. Although the risks are exceedingly low in older patients with no current or past history of substance abuse, it is impossible to identify every patient who will abuse or divert prescribed opioids [117]. Therefore, many clinicians have adopted a Universal Precautions approach to pain management [118]. This paradigm stresses that every patient should be assessed for risk factors related to the potentially problematic use of pain medication. Such an approach seeks to protect patients from the harm of substance abuse and helps primary care providers meet their legal and regulatory responsibilities. Various sources, including published guidelines and statements from state medical boards, are available to help clinicians assess and monitor patients with persistent pain for responsible opioid use (Table 4) [119,120].

Table 4 Available resources for published guidelines and statements from state medical boards for responsible opioid treatment regimens

Society	Link to Resources
American Academy of Pain Medicine	http://www.painmed.org/clinical_info/guidelines.html
American Pain Society	http://www.ampainsoc.org/pub/cp_guidelines.htm http://www.ampainsoc.org/links/clinician1.htm
Federation of State Medical Boards	http://www.fsmb.org/RE/PAIN/resource.html
American Academy of Pain Management	http://www.aapainmanage.org/literature/publications.php

For an initial risk assessment, tools such as the Opioid Risk Tool (ORT) [121] and the revised version of the Screener and Opioid Assessment for Patients with Pain (SOAPPR) [122] are available to help determine the presence of risk factors known to be associated with problematic drug use. The ORT is a brief, validated questionnaire that assigns a sex-specific score to patients based on five general risk factors for future aberrant opioid-related behaviors. These risk factors are a personal history of substance abuse, a family history of substance abuse, relatively young age, mental illness, and a history of preadolescent sexual abuse [121]. The 24-item SOAPP-R was empirically derived from an initial pool of 142 conceptually predictive indicators of, or risk factors for, future aberrant opioid use [122]. Scores on the ORT and the SOAPP-R are used to stratify patients as low, medium, or high risk, which in turn informs their treatment plan. Patients who have already been prescribed opioid medications can be assessed using the Current Opioid Misuse Measure, a 17-question self-assessment designed to identify ongoing patient misuse of opioid medication [123]. These tools should be used to supplement a physical examination, patient interviews, the healthcare provider's clinical experience, and diligent monitoring as a component of a comprehensive initial and ongoing risk assessment. The patient interview may help to validate claims of pain, explore drug and alcohol use, and determine the safety of opioids within the patient's home while also helping to identify potential risk factors in treatment.

Stratification of patients is not meant to deny treatment to those classified as being at high risk for abuse. Rather, it allows the clinician to consider who can be treated without consultation, who should be co-managed with the assistance of a

specialist, and who should be referred to medical providers with extensive experience in pain medicine or addiction medicine [107].

Although clinicians should remain vigilant about the possibility of misuse or abuse of opioid agents in all patients irrespective of age, older age is significantly associated with lower risk for opioid misuse and abuse [112,113,124,125]. Some authors suggest that underuse of opioids in older populations constitutes a greater problem [126]. Given that older patients may not fill prescriptions or may take opioid medications sparingly because of multiple concerns (e.g., fear of addiction, costs, fear of constipation, negative social stigma), clinicians are encouraged to query patients about their beliefs and prior experiences with this class of medications before beginning an opioid medication.

Adjuvant Drugs

A number of drugs from various classes that were developed for purposes other than pain relief have been found in traditional experimental pain models to alter or attenuate pain perception in many pain-producing conditions without raising the pain threshold. These agents, now conventionally termed adjuvant drugs, originally appeared in the cancer pain literature, although the term is now used regardless of pain etiology [127]. Drug classes include antidepressants, anticonvulsants, and other agents that alter neural membrane potentials, ion channels, cell surface receptor sites, synaptic neurotransmitter levels, and other neuronal processes involved in pain signal processing. Adjuvant drugs may be used alone or co-administered with nonopioid or opioid analgesics and are used in a variety of persistent pain conditions, especially neuropathic pain.

Tricyclic antidepressants (including amitriptyline, desipramine, and nortriptyline) were the first drugs found to reduce pain associated with postherpetic neuralgia and painful peripheral diabetic neuropathy, but the adverse-effect profile of this class of drugs often contraindicates their use in older patients. More recent pharmacological advances in the treatment of depression have included selective serotonin-reuptake inhibitors (SSRIs) and mixed serotonin- and norepinephrine-uptake inhibitors (SNRIs). The SNRIs (duloxetine, venlafaxine) are particularly effective in the treatment of various neuropathic pain conditions and fibromyalgia, with a better side-effect profile than the tricyclic antidepressants. In contrast, SSRI drugs (sertraline, fluvoxamine, fluoxetine, citalopram) have not proved to be effective against pain. Gabapentin, pregabalin, and other anticonvulsant agents with similar mechanisms of action at voltage-gated calcium ion channels have been found to have beneficial effects in various neuropathic pain conditions more-benign side-effect profiles than older anticonvulsant and antidepressant tricyclic drugs [128–133].

To minimize adverse effects, all pain-modulating drugs must be carefully titrated and monitored frequently. Regular phone contact and follow-up visits should be scheduled to assess therapeutic effects and monitor for adverse reactions.

Other Drugs for Pain

Anecdotal evidence and a limited number of studies have indicated that other drugs, as a group, are less reliable than opioids and traditional analgesics in the treatment of persistent pain. These observations are often based on small patient populations in which subjects may be less responsive to other drugs or have a higher likelihood for side effects or a slower onset of action (in some cases related to the need for long titration periods to avoid side effects). In the absence of data from well-controlled clinical trials that are easily applicable to a given clinical situation, the use of these nonopioid, nontraditional drugs is largely a matter of clinical judgment [134].

Corticosteroids

Analgesic effects have been described for a variety of systemically administered corticosteroids in a broad range of dosages for a variety of conditions. Effective use has been documented for rheumatic and autoimmune arthropathies and vasculidities, including rheumatoid arthritis, polymyalgia rheumatica, giant cell arteritis, other autoimmune disorders, and acute crystal-induced arthropathies. Efficacy has also been suggested for some neuropathic pain syndromes (sympathetic dystrophies); cancer pain, including bone pain, infiltration, or compression of nerves; headache due to intracranial pressure; and pain related to bowel obstruction [135]. Current evidence is unable to clearly differentiate between corticosteroids in terms of acute or long-term efficacy or dose-response relationships. The well-known side effects and serious toxicity of short- and long-term use of corticosteroids often limit their overall safety to lowdose, short-term administration or use in patients near the end of life.

Muscle Relaxants

Muscle relaxant drugs include cyclobenzaprine, carisoprodol, chlorzoxazone, methocarbamol, and others. Cyclobenzaprine is essentially identical to amitriptyline, with potential adverse effects similar to those of amitriptyline. In addition, carisoprodol has been removed from the European market because of concerns about drug abuse. Although these drugs may relieve skeletal muscle pain, their effects are nonspecific and not related to muscle relaxation [134]. Therefore, they should not be prescribed in the mistaken belief that they relieve muscle spasm. Muscle relaxants may inhibit polysynaptic myogenic reflexes in animal models, but whether this is related to pain relief remains unknown. If muscle spasm is suspected to be at the root of the patient's pain, it is probably justified to consider another drug with known effects on muscle spasm (e.g., benzodiazepines, baclofen). Clinicians should be aware that many of these drugs may be associated with greater risk for falls in older persons.

Baclofen is an agonist of the gamma amino butyric acid type B. Although its efficacy has been documented as a second-line drug for paroxysmal neuropathic pain, it has been used in patients with severe spasticity as a result of central nervous system injury, demyelinating conditions, and other neuromuscular disorders [136]. Starting with a low dose and gradually increasing the prescribed amount may minimize the common side effects of dizziness, somnolence, and gastrointestinal symptoms. Discontinuation after prolonged use requires a slow tapering period because of the potential for delirium and seizure.

Benzodiazepines

The efficacy of benzodiazepines in the management of persistent pain is limited. Current information does not support a direct analgesic effect of these drugs [137]. The high risk profile in older adults usually obviates any potential benefit that such agents might render in terms of pain relief, although they may be justified for management of anxiety (particularly in the setting of delivering end-of-life care) or in a trial for relief of muscle spasm, especially in common situations in which anxiety, muscle spasm, and pain coexist.

Calcitonin and Bisphosphonates

Calcitonin may be helpful in various cases of bone pain and as a second-line treatment for some neuropathic conditions. Studies have suggested that calcitonin may relieve pain resulting from postosteoporotic vertebral compression fractures and pelvic fractures and in cancer patients with bone metastases [138,139]. The mechanism by which calcitonin relieves pain remains unknown. Apart from hypersensitivity reactions, the main side effects of calcitonin are nausea and altered serum levels of calcium and phosphorus. Therefore, assessment of calcium and phosphorus may be advisable.

Bisphosphonates may also provide analgesia in patients with cancer with metastases, particularly in those with breast or prostate cancer or multiple myeloma. Data are promising for pamidronate and clodronate [140]. Other drugs in this class have low potency or have not been studied. Side effects of bisphosphonates are usually related to nausea, esophagitis, or occasional hypocalcemia.

Topical Analgesics

Literature reviewed for this publication indicates that randomized, placebo-controlled trials of the lidocaine 5% patch have been limited to the treatment of neuropathic pain. Evidence suggests that the lidocaine 5% patch is effective in cases of postherpetic neuralgia, but the observed benefit does not usually compare with that of systemic gabapentin or tricyclic antidepressants [141]. Fewer controlled data are available for the lidocaine patch in other neuropathic conditions or in non-neuropathic pain. Since receiving FDA approval for the treatment of postherpetic neuralgia, the patch has been used widely off label for other neuropathic conditions, diabetic neuropathies, chronic low back pain, osteoarthritis, bone metastasis, and even chronic wounds, despite direct warnings by the manufacturer against its use in wound care. The rapid adoption of this product is related to its ease of use, absence of toxicity, and lack of drug interactions. Pharmacokinetic studies have shown that systemic lidocaine levels remain within a safe range with doses of up to four patches in 24 hours. Adverse reactions are rare, mild, and mostly related to skin rash. The patch is contraindicated in advanced liver failure because of decreased lidocaine clearance.

Eutectic mixture of lidocaine and prilocaine (EMLA) is a mixture of the local anesthetics prilocaine and lidocaine. EMLA is capable of penetrating the skin to form a local cutaneous anesthesia and is often used to prevent the pain of needle puncture or incision [142]. There is a risk of systemic toxicity if used repeatedly or near mucus membranes or open wounds.

Topical capsaicin cream has been shown to provide some benefit in the reduction of neuropathic and nonneuropathic pain [143,144], although 30% of patients may not be able to tolerate the burning sensation associated with treatment initiation. This burning sensation may persist for several months. Observations suggest that depletion of substance P, with resulting analgesia, may require several weeks of continuous exposure. For this reason, prolonged trials may be needed for some patients. Newer formulations that also contain aspirin, NSAIDs, local anesthetics, or tricyclic antidepressant preparations may help ameliorate the burning sensation and reduce premature treatment cessation.

Topical NSAIDs have shown some efficacy in a few studies of persistent pain management [145,146]. Studies of topical aspirin, indomethacin, diclofenac, piroxicam, and ketoprofen have reported mixed results in neuropathic and nonneuropathic pain syndromes. Currently there are two diclofenac topical preparations that have received FDA approval for pain management. Systemic absorption appears to be minimal when these agents are used in recommended doses, and although the reported toxicity seems to be low, the biology of these agents is not fully understood. Randomized, placebo-controlled trials have demonstrated that the benefit is not simply a placebo effect related to the soothing sensation of rubbing cream onto a painful area.

Cannabinoids

Antinociceptive effects have been observed with the use of cannabinoids in animal models and in a few controlled clinical trials of humans with persistent pain [147–149]. In older patients, the therapeutic window for cannabinoids appears to be narrow because of the dysphoric response that older patients and those using higher doses may experience.

Guideline Recommendations

Nonopioids

(I) Acetaminophen should be considered as initial and ongoing pharmacotherapy in the treatment of persistent pain, particularly musculoskeletal pain, owing to its demonstrated effectiveness and good safety profile (high quality of evidence; strong recommendation).
  (A) Absolute contraindications: liver failure (high quality of evidence, strong recommendation).
  (B) Relative contraindications and cautions: hepatic insufficiency, chronic alcohol abuse or dependence (moderate quality of evidence, strong recommendation).
  (C) Maximum daily recommended dosages of 4 g per 24 hours should not be exceeded and must include "hidden sources" such as from combination pills (moderate quality of evidence, strong recommendation).

(II) Nonselective NSAIDs and COX-2 selective inhibitors may be considered rarely, and with extreme caution, in highly selected individuals (high quality of evidence, strong recommendation).
  (A) Patient selection: other (safer) therapies have failed; evidence of continuing therapeutic goals not met; ongoing assessment of risks and complications outweighed by therapeutic benefits (low quality of evidence, strong recommendation).
  (B) Absolute contraindications: current active peptic ulcer disease (low quality of evidence, strong recommendation), chronic kidney disease (moderate level of evidence, strong recommendation), heart failure (moderate level of evidence, weak recommendation).
  (C) Relative contraindications and cautions: hypertension, *Helicobacter pylori*, history of peptic ulcer disease, concomitant use of corticosteroids or SSRIs (moderate quality of evidence, strong recommendation).

(III) Older persons taking nonselective NSAIDs should use a proton pump inhibitor or misoprostol for gastrointestinal protection (high quality of evidence, strong recommendation).

(IV) Patients taking a COX-2 selective inhibitor with aspirin should use a proton pump inhibitor or misoprostol for gastrointestinal protection (high quality of evidence, strong recommendation).

(V) Patients should not take more than one nonselective NSAID or COX-2 selective inhibitor for pain control (low quality of evidence, strong recommendation).

(VI) Patients taking aspirin for cardioprophylaxis should not use ibuprofen (moderate quality of evidence, weak recommendation).

(VII) All patients taking nonselective NSAIDs and COX-2 selective inhibitors should be routinely assessed for gastrointestinal and renal toxicity, hypertension, heart failure, and other drug–drug and drug–disease interactions (weak quality of evidence, strong recommendation).

Opioids

(VIII) All patients with moderate to severe pain, pain-related functional impairment, or diminished quality of life due to pain should be considered for opioid therapy (low quality of evidence, strong recommendation).

(IX) Patients with frequent or continuous pain on a daily basis may be treated with around-the-clock timecontingent dosing aimed at achieving steady-state opioid therapy (low quality of evidence, weak recommendation).

(X) Clinicians should anticipate, assess for, and identify potential opioid-associated adverse effects (moderate quality of evidence, strong recommendation).

(XI) Maximal safe doses of acetaminophen or NSAIDs should not be exceeded when using fixed-dose opioid combination agents as part of an analgesic regimen (moderate quality of evidence, strong recommendation).

(XII) When long-acting opioid preparations are prescribed, breakthrough pain should be anticipated, assessed, and prevented or treated using short-acting immediate-release opioid medications (moderate quality of evidence, strong recommendation).

(XIII) Only clinicians well versed in the use and risks of methadone should initiate it and titrate it cautiously (moderate quality of evidence, strong recommendation).

(XIV) Patients taking opioid analgesics should be reassessed for ongoing attainment of therapeutic goals, adverse effects, and safe and responsible medication use (moderate quality of evidence, strong recommendation).

Adjuvant Analgesic Drugs

(XV) All patients with neuropathic pain are candidates for adjuvant analgesics (strong quality of evidence, strong recommendation).

(XVI) Patients with fibromyalgia are candidates for a trial of approved adjuvant analgesics (moderate quality of evidence, strong recommendation).

(XVII) Patients with other types of refractory persistent pain may be candidates for certain adjuvant analgesics (e.g., back pain, headache, diffuse bone pain, temporomandibular disorder) (low quality of evidence, weak recommendation).

(XVIII) Tertiary tricyclic antidepressants (amitriptyline, imipramine, doxepin) should be avoided because of higher risk for adverse effects (e.g., anticholinergic effects, cognitive impairment) (moderate quality of evidence, strong recommendation).

(XIX) Agents may be used alone, but often the effects are enhanced when used in combination with other pain analgesics and nondrug strategies (moderate quality of evidence, strong recommendation).

(XX) Therapy should begin with the lowest possible dose and increase slowly based on response and side effects, with the caveat that some agents have a delayed onset of action and therapeutic benefits are slow to develop. For example, gabapentin may require 2 to 3 weeks for onset of efficacy (moderate quality of evidence, strong recommendation).

(XXI) An adequate therapeutic trial should be conducted before discontinuation of a seemingly ineffective treatment (weak quality of evidence, strong recommendation).

Other Drugs

(XXII) Long-term systemic corticosteroids should be reserved for patients with pain-associated inflammatory disorders or metastatic bone pain. Osteoarthritis should not be considered an inflammatory disorder (moderate quality of evidence, strong recommendation).

(XXIII) All patients with localized neuropathic pain are candidates for topical lidocaine (moderate quality of evidence, strong recommendation).

(XXIV) Patients with localized nonneuropathic pain may be candidates for topical lidocaine (low quality of evidence, weak recommendation).

(XXV) All patients with other localized non-neuropathic persistent pain may be candidates for topical NSAIDs (moderate quality of evidence, weak recommendation).

(XXVI) Other topical agents, including capsaicin or menthol, may be considered for regional pain syndromes (moderate quality of evidence, weak recommendation).

(XXVII) Many other agents for specific pain syndromes may require caution in older persons and merit further research (e.g., glucosamine, chondroitin, cannabinoids, botulinum toxin, alpha-2 adrenergic agonists, calcitonin, vitamin D, bisphosphonates, ketamine) (low quality of evidence, weak recommendation).

Panel Members and Affiliations

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