ABSTRACT

Background: By 2030, the US population of adults aged ≥65 years will increase by >80%, and these adults will account for nearly 20% of the US population. In this population, the decline of multiple physiologic processes and diseases collectively influence treatment options. Physiologic changes, drug–drug interactions resulting from polypharmacy, and drug–disease interactions combine to make elderly patients more sensitive to the adverse events (AEs) associated with medications, all of which must be considered in drug selection.

Objective: This article focuses on select underutilized medication options for analgesia that may provide significant advantages in the elderly population above and beyond commonly prescribed conventional choices.

Methods: We performed a complete review of the literature using the search terms pain management, elderly, opioids, NSAIDs, topical NSAIDs, levorphanol, buprenorphine transdermal, and tapentadol. Databases searched included PubMed, Google Scholar, Ovid, and Athens. Package inserts were utilized for approval dates, indications, and formulations available. We looked at reviews of agents to identify important studies for consideration that searches may have missed. Pharmacology and pharmacokinetic data were taken from randomized trials focusing in this area. Pivotal Phase III trials were utilized for discussion of clinical trial experience and to summarize efficacy and AEs. For purposes of validity, only peer-reviewed literature was included.

Results: There were limited data that specifically outlined analgesic drug selection and highlighted safer alternatives for the elderly patient based on polypharmacy risks, end-organ deterioration, and/or drug choices that presented less risk. We focused on unique opioid alternatives: levorphanol, which offers several therapeutic advantages similar to methadone but without the pharmacokinetic and drug–interaction pitfalls associated with methadone; tapentadol, associated with significantly less gastrointestinal distress and constipation; and transdermal buprenorphine, an agonist/antagonist with less risk for the toxicities associated with conventional opioids and with compliance benefits. Topical NSAIDs are discussed as a viable therapeutic option. Specific attention to a more desirable tolerability profile, including avoidance of drug interactions, end-organ dysfunction, and gastrointestinal bleed with topical NSAID agents versus their oral counterparts is discussed, including the ability to achieve superior tissue levels for appropriately selected inflammatory conditions.

Conclusion: It is incumbent that providers consider these options as part of an analgesic armamentarium in an effort to maximize therapeutic benefit and minimize risks in the increasing elderly patient population. (Clin Ther. 2013;35:1669–1689) Published by Elsevier HS Journals, Inc.

Key words: analgesia, buprenorphine transdermal, elderly, levorphanol, opioids, pain management, tapentadol, topical NSAIDs.
INTRODUCTION
Over the next 15 years, the number of adults aged ≥65 years will increase by 80% and account for nearly 20% of the total population. "Baby boomers," born between 1949 and 1964, will reach age 65 years, and the elderly will compose the largest percentage of the total population. The fastest-increasing age group is that aged ≥85 years as life expectancy continues to increase, with average life expectancies of 80.8 years in women and 75.7 years in men. It is vital that health care professionals familiarize themselves with this unique population and employ evidence-based treatment strategies shown to ensure maximum efficacy and tolerability.

The decline of multiple physiological processes (Table I), even in the absence of disease, combined should logically influence treatment options. Decreased gastric secretions, intestinal motility, and vitamin D receptors lead to loss of appetite, malnutrition, and decreased bone density. Increased arterial thickening and rigidity elevate cardiac risk, while decreased elasticity in the lungs potentially exacerbates breathing disorders. Memory impairment and cognitive decline progress as neurons become less resilient to stress over time. Reduced hepatic and renal blood flow limit metabolism and filtration, increasing the risk for accumulation of toxic substances. In fact, 49% of all hospitalizations attributed to the adverse events (AEs) associated with medications occur in the elderly. Physiologic changes, drug–drug interactions resulting from polypharmacy, and drug–disease interactions combine to make elderly patients more sensitive to the AEs of medications.

Effective pain management in the elderly is challenging. The elderly may be afflicted with a myriad of painful conditions, including osteoarthritis, degenerative joint disease, rheumatoid disorders, cancer, post-herpetic neuralgia, fibromyalgia, and diabetic neuropathy. According to the Institute of Medicine, although pain is the most common reason for physician consultation, nearly 100 million Americans have chronic pain. The clinical concern for AEs among the elderly places them at increased risk for undertreatment of their pain.

The purpose of this review is to highlight the use of several treatment options that are underutilized despite demonstrated advantages in the general population, but most particularly in elderly patients. Opioids, for example, may actually afford the safest alternative in many cases in elderly patients compared to oral anti-inflammatories, certain antidepressants, or anticonvulsants. Moreover, the unique pharmacology of certain opioids make them advantageous in certain painful disorders frequently encountered within this

| Table I. Summary of physiologic changes with aging. |
|-------------|---------------------------------------------------|
| **Organ System** | **Changes** |
| General | Body fat ↑, muscle mass ↓, total body water ↓ |
| Musculoskeletal | Arthritis ↑, myalgias ↑ |
| Cardiovascular | Ejection fraction ↓, cardiac output ↓, response to β-adrenergic stimuli ↓, arterial wall thickness ↑, elastin ↓, endothelial nitric oxide synthetase activity ↓, arterial distensibility ↓, vascular inflammation and thrombotic events ↑ |
| Respiratory | Chest wall rigidity ↑, functional residual capacity (FRC) ↑, elastic recoil ↓, ventilation/perfusion mismatch ↑ |
| Gastrointestinal | Transit time ↑, amount of lymphoid tissue ↓, vitamin D receptors ↓ |
| Hepatic | Liver cells ↓, blood flow to the liver ↓ |
| Renal | Blood flow ↓, eGFR ↓, accuracy of calculating GFR ↓ |
population. We present evidence to support the use of each agent discussed, but have selected these specific treatment options also based on experience in our pain clinic. The following discussion is not intended as an endorsement of any medication and, as always, treatment should be patient specific.

MATERIALS AND METHODS
We performed a complete review of the literature using the search terms pain management, elderly, opioids, NSAIDs, topical NSAIDs, levorphanol, buprenorphine transdermal, and tapentadol to ascertain which analgesic drugs are most commonly used in the elderly population. Databases searched included PubMed, Google Scholar, Ovid, and Athens. There were limited data that specifically outlined analgesic drug selection and highlighted safer alternatives for the elderly patient based on polypharmacy risks, end-organ deterioration, and/or drug choices that specifically presented less risk for any of these reasons. We included meta-analyses, randomized studies, case reports, commentaries, and case-control studies of all analgesics searched. Package inserts were utilized for approval dates, indications, and formulations available. We looked at reviews of agents to identify important studies for consideration that searches may have missed. Pharmacology and pharmacokinetic data were taken from randomized trials focused on the elderly patient based on polypharmacy risks, end-organ deterioration, and/or drug choices that specifically presented less risk for any of these reasons. We included meta-analyses, randomized studies, case reports, commentaries, and case-control studies of all analgesics searched. Package inserts were utilized for approval dates, indications, and formulations available. We looked at reviews of agents to identify important studies for consideration that searches may have missed. Pharmacology and pharmacokinetic data were taken from randomized trials focused on this area, whereas other references helped point us in the right direction. Pivotal Phase III trials were utilized for discussion of clinical trial experience and to summarize efficacy and AEs. Case reports were not relied on except for in the examination of references.

In terms of organization, we introduce each agent, year of FDA approval, currently approved indications, and available formulations. We review relevant pharmacology and pharmacokinetics that make each particular agent unique, convey understanding of how it works, provide evidence-based data supporting unique characteristics, and specifically highlight issues such as drug interactions that are particularly notable in this subject and population. Clinical trials focused on efficacy and tolerability, age of the population studied, discontinuation rates, and any other pertinent analysis are summarized. Finally, we summarize how all of these issues collectively and individually could be significantly advantageous in the elderly population.

RESULTS
Diclofenac Epolamine 1.3% Topical Patch
Use of NSAIDs in the elderly population, beyond that seen in the general population, is complicated by the substantial risks for gastrointestinal (GI) bleed, ulcerations, perforations, nephrotoxicity, and cardiovascular morbidity and mortality. The prevalence of serious GI AEs with oral NSAIDs is 15%, and GI events are at least twice as likely in people aged > 60 years. A recent study by the Coxib and Traditional NSAID Trialists’ Collaboration confirmed these risks and suggested that serious GI and cardiovascular AEs may be dose and plasma concentration dependent. Consequently, prescribers frequently avoid one of the most effective therapeutic medication classes in the elderly specifically due to safety concerns. The past decade has seen an effort to provide NSAID therapy with increased tolerability in elderly patients, with a shift from oral to topical NSAIDs. In fact, in 2006, topical NSAIDs were recommended therapies in 7 of 9 published guidelines. Limitations of topical NSAIDs include cost, erratic local absorption, variable depth of penetration, inaccuracy of dosing, variable wear times that may require frequent applications, and an uncomfortable oleaginous feeling.

An estimated 50% of all NSAID prescriptions are written for osteoarthritis. Osteoarthritis is the most prevalent pain condition in the United States, affecting 27 million people, and is also the most commonly diagnosed type of arthritis. Approximately 10 million (38%) people with osteoarthritis are aged ≥ 60 years, and this number is expected to reach 67 million by 2030 because of the aging population. Diclofenac is by far the most utilized NSAID worldwide and has become available in > 100 countries since its introduction in 1974. Diclofenac is currently available in several topical gels and 1 topical solution. In 2007, the diclofenac epolamine 1.3% topical patch (DETP) was FDA approved for the topical treatment of acute pain due to minor sprains, strains, and contusions. In contrast, the patch has been approved in Europe since 1993 and was available in 43 countries in 2008, and studies suggest significant pain relief in chronic
conditions such as knee osteoarthritis and epicondylitis (tennis elbow). 19–21 In a pooled analysis of 5 DTEP trials in acute injuries, efficacy over placebo was shown in terms of pain control in the back, shoulder, foot, and elbow as measured on a visual analog scale (VAS). 18

The DETP patch affords steady drug concentrations directly at the site of injury. The topical patch was designed as a drug-in-matrix system impregnated with diclofenac 180 mg containing 129.7 mg of diclofenac acid (comparable to 140 mg diclofenac sodium) and 50.3 mg of epolamine salt. 22–24 Epolamine salt is used to increase cell permeability by solubilizing lecithin, a major constituent of cell membranes, thereby increasing its hydrophilic and lipophilic potencies. 22,23 The distinction between topical and transdermal patches is important: Topical dosage formulations are meant to penetrate skin and tissue but not enter into the plasma in significant concentrations, whereas transdermal products are designed to achieve therapeutic concentrations in systemic circulation, merely using cutaneous tissue as a vehicle for delivery. 15,21,22 At the end of the 12-hour dosing interval, 5% of the total diclofenac dose is absorbed into the tissue; after 24 hours of DETP exposure, 18 mg have potentially been released from the patch. 23

In terms of pharmacokinetics, the oral terminal half-life of diclofenac is 1 to 2 hours, whereas the half-life remains 9 to 12 hours with the topical patch, indicating local drug accumulation within a tissue reservoir. 22,23,26 Diclofenac accumulation beneath the patch allows for greater local tissue concentrations with topical NSAIDs compared with oral NSAIDs. 22,27–29 Other factors contributing to lower diclofenac tissue concentrations after oral compared with topical administration include high protein binding (99%), extensive first-pass metabolism (≈ 50%), and a low volume of distribution (1.3 L/kg). 17 Studies have shown that pain relief occurs as early as 1 hour after DETP placement, but minimal plasma concentrations appear 2 to 8 hours after patch application, depending on the rate of cutaneous absorption, which can be highly variable among individuals. 11,22 Some patients may not respond at all, presumably at least in part due to lack of skin penetration and penetration depth. 30 The systemic exposure of DETP is 1% of oral exposure following a 75-mg oral diclofenac dose. 22 The steady-state plasma concentrations are also significantly lower (1–3 ng/mL) and therefore are unlikely to result in cyclooxygenase-1–mediated effects that interfere with platelet aggregation or compromise gastric protection. 17 For example, the minimum concentration of diclofenac necessary to inhibit platelet aggregation was 300 ng/mL (4%) by arachidonic assay. 22 At 400 ng/mL, diclofenac can reduce platelet aggregation by 41%. 22 The low plasma concentrations result in an improved tolerability profile and increased attractiveness for utilization in elderly patients. 21,22

Although disingenuous, the FDA requires that manufacturers incorporate standard NSAID precautions into the labeling despite stating in their own medical review that 100 patches worn simultaneously would equal 1 diclofenac oral dose of 150 mg. 26 In clinical trials, the most common AEs reactions were cutaneous application-site reactions (pruritus, burning), which occurred more with placebo (8%, 1%) than with treatment (5%, <1%), and which, in the authors’ opinion, most likely were a result of the anti-inflammatory effect of DETP. 17 The only GI event reported was nausea, the prevalence of which was not statistically different versus placebo. 21,31 From 1993 to 2008, postmarketing surveillance revealed that >6 million patients worldwide received the DETP and that AEs were reported in 108 patients, the majority of which were skin reactions or lack of efficacy. Six were serious GI events (bleeding or ulcer), none of which demonstrated a causal relationship to DETP. 21

DETP is an attractive option for targeted and consistent drug delivery over a specific area, with few or no AEs. As a class, topical NSAIDs are effective and underutilized and compare well against other therapeutic options. The Osteoarthritis Research Society International published a meta-analysis in 2010 to evaluate and compare available treatment options for hip and knee osteoarthritis. 14 Therapeutic options were assigned an effect size based on the published literature. Opioids and intra-articular corticosteroid injections provided more pain relief, yet topical NSAIDs were more effective in improving function and stiffness, with a more favorable AE profile (Figure 1). Compared with acetaminophen, the most commonly used medication for osteoarthritis pain, topical NSAIDs provide 3 times the effect size in pain relief, improved function, and reduced stiffness. 14 Topical NSAIDs cannot target central and peripheral pain mechanisms like oral NSAIDs, and they are inappropriate for neuropathic pain, widespread musculoskeletal pain, and chronic low back pain
due to boney arthritis (vs muscle spasm), in which penetration may be inadequate.\textsuperscript{30,32} For many elderly patients unable to use oral NSAIDs, topical NSAIDs, including DTEP, should be considered to provide targeted pain relief, reduce stiffness, maximize function, and mitigate oral NSAID risks.

**Levorphanol**

Levorphanol is the “forgotten opioid” and perhaps is not prescribed nearly often enough in the hospice and palliative-care settings or for neuropathic pain syndromes requiring opioids.\textsuperscript{33,34} Despite being available for use in the United States since 1953, it is relatively unknown or unfamiliar to the majority of today’s prescribers.\textsuperscript{35} The complex pharmacokinetics of, and lack of experience among contemporary practitioners with, levorphanol diminish its usability as a first-line agent, yet its unique attributes could fill an important niche in the management of pain. For elderly patients with persistent neuropathic pain, levorphanol can be particularly useful, especially as an alternative to methadone, the use of which has recently increased for this same indication.\textsuperscript{33,36}

Use of opioids for chronic noncancer pain remains controversial for a variety of reasons, including mixed evidence, risk for addiction, increasing opioid-related drug overdoses (especially when polypharmacy is a factor), and lack of long-term efficacy and tolerability data.\textsuperscript{37–42} An increased emphasis on the undertreatment of pain in the 1990s spurred significant research into its mechanisms and resulted in increased opioid prescribing.\textsuperscript{43,44} One result of this effort was the characterization of N-methyl-D-aspartate (NMDA) receptors and their role in both chronic, but more particularly neuropathic, pain.\textsuperscript{34} Neuronal hyperexcitability and overstimulation leads to excitatory signals from L-glutamate and L-aspartate, which activate NMDA receptors, the results of which could be hyperalgesia, allodynia, and potential neuroplasticity.\textsuperscript{45,46} In vitro and animal models have demonstrated that antagonizing NMDA receptors can theoretically reverse the aspects of chronic pain and neuronal hyperexcitability, and potentially mitigate opioid tolerance.\textsuperscript{46–50} An enormous research effort into NMDA antagonists, particularly ketamine, high-dose dextromethorphan, and memantine, followed. The results have been mixed in clinical trials because treatment-emergent AEs are often encountered before any therapeutic benefit. One such combination, morphine/dextromethorphan, made it to Phase III trials before lack of benefit and psychological AEs led to discontinuation.\textsuperscript{51} The NMDA receptor inhibition of several opioids have been studied, and while most demonstrate no activity, some of the dehydroxylated phenanthrenes of the morphinan type and their enantiomers (levorphanol, dextrorphan, levomethorphan, dextromethorphan), as well as the diphenylheptanes (methadone, propoxyphene), appear to have considerable affinity for NMDA receptors.\textsuperscript{47}

Levorphanol is mechanistically similar to methadone; both are potent agonists of the \(\mu\)-opioid receptor, both are noncompetitive antagonists at the NMDA receptor, and both inhibit the reuptake of serotonin (5-HT) and norepinephrine (NE).\textsuperscript{34,52–54} There are, however, differences. Levorphanol is a more potent NMDA antagonist, similar to ketamine, with greater affinity for the NMDA and \(\mu\)-opioid receptors. Levorphanol has decreased affinity for the 5-HT and NE receptors compared with methadone.\textsuperscript{47,52} But

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**Figure 1.** Effect size of pharmacologic intervention in knee osteoarthritis. IA = Intra-articular.\textsuperscript{14}
Unlike methadone, levorphanol is also considered a full agonist at the \( \kappa \)-opioid receptor, with high affinity for the \( \kappa_1 \) and \( \kappa_3 \) receptor subtypes. \( \kappa_3 \) is believed to be the primary \( \kappa \) receptor involved in analgesic activity.\(^{55}\) \( \kappa \) receptors are associated with dysphoria and sedation yet are theorized to have fewer overall AEs. However, at this time, there are no available selective antagonists for the \( \kappa \) receptor.\(^{54,56}\)

Levorphanol is roughly 4 to 8 times more potent than morphine and is available as a 2-mg tablet.\(^{33,35}\) It is 40% protein bound and crosses the blood–brain barrier with cerebral spinal fluid concentrations of 60% to 70% of corresponding plasma concentrations.\(^{57}\) The half-life (11–16 hours) of levorphanol is longer than its duration of analgesia (6–15 hours), allowing for potential drug accumulation with long-term dosing until steady-state concentrations are reached (80 hours).\(^{57}\) This obstacle is similar to that seen with methadone but is not nearly as problematic with regard to cytochrome P450 (CYP) metabolism. Nonetheless, dose increases are not recommended more frequently than every 4 days, and although levorphanol is typically dosed every 6 to 8 hours, the interval may need to be extended in the setting of hepatic or renal impairment, where drug accumulation is possible (Table II). Accumulation is a more significant problem with methadone, as the disparity between its duration of analgesia (8–12 hours) and variable half-life (15–60 hours) could easily result in drug overdose, particularly if one adds doses for breakthrough pain while the methadone continues to sequester within body tissues because of its high volume of distribution.\(^{34,60}\)

In 2009, methadone represented 2% of all written prescriptions for opioids but >30% of opioid-related deaths—more than twice the amount with any other opioid.\(^{61}\) There were nearly 6 times as many methadone overdose deaths in 2010 as there were in 1999, and this increase was driven mainly by an increase in prescriptions for pain.\(^{62}\) The risk for drug accumulation is countered by patience in titration and dose adjustments and does not alone account for the serious risks of methadone. Three key factors make methadone particularly dangerous. First, methadone undergoes 3A4 (and other isozyme) metabolism via the hepatic CYP system, leading to a myriad of drug–drug interactions that can potentially increase methadone serum concentrations to unsafe levels.\(^{35,60}\) Second, methadone can prolong the QTc interval, leading to life-threatening cardiac arrhythmias, especially when combined with other proarrhythmic drugs.\(^{35,53}\) Third, methadone is a P-glycoprotein substrate, which was elucidated recently to have clinically significant interactions with HIV treatments and other medications, coupled with enhanced passage through P-glycoprotein–dependent transfer across the blood–brain barrier.\(^{63}\) Consider the genetic polymorphic differences in any patient population with its resultant variability, and methadone may make even the most experienced practitioners nervous. In contrast, levorphanol metabolism is similar to other dehydroxylated phenanthrenes (oxycodone, hydromorphone, oxymorphone, hydrocodone) in that it results in a 3-glucuronide product that is renally excreted. Levorphanol is not metabolized by the CYP system, lacks the cardiac toxicity associated with methadone, and is not a known substrate of P-glycoprotein. As a result, levorphanol presents several advantages over methadone in any patient, but particularly in elderly patients receiving multiple medications.\(^{33,37,60-63}\)

Rowbotham et al\(^{36}\) studied levorphanol in 81 patients with neuropathic pain in an 8-week randomized, double-blind study in which the median patient age was 65 years (range, 32–91 years). Patients were allowed to self-titrate according to reduction in pain and occurrence of AEs within specified dosing limits identified for safety. Patients were randomized to low-dose (mean, 2.7-mg/d) or high-dose (mean, 8.9-mg/d) therapy, with a primary end point of overall reduction in pain, as measured using a visual analog scale (VAS) ranging from 0 to 100. A 36% overall reduction in pain scores was reported in the high-dose group; 21% reduction in the low-dose group. Older age or earlier onset of pain did not correlate with a smaller reduction in pain scores. A total of 59 patients (73%) completed the study, 12 of 15 (80%) of those who withdrew due to AEs were in the high-dose group, 3 patients reportededly withdrew due to lack of efficacy, and 7 of the 10 patients with central pain after stroke or focal brain injury did not complete the study. Considering that the investigators allowed participants to continue treatment with antidepressants (30%), NSAIDs (30%), and anticonvulsants (14%), the overall pain reductions represent efficacy above and beyond standard therapy for neuropathic pain. Investigators monitored as patient pain scores returned to baseline following study completion and levorphanol taper which strongly indicates treatment efficacy.\(^{36}\) Armed with an appreciation for the
<table>
<thead>
<tr>
<th>Pharmacology</th>
<th>Levorphanol $^{33,35,36,47,52,57-59}$</th>
<th>Methadone $^{47,52,58-60}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacological activity</td>
<td>$\mu, \kappa_1, \kappa_3 \gg \kappa_2$</td>
<td>$\mu$</td>
</tr>
<tr>
<td>NE reuptake inhibition</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td>NMDA inhibition</td>
<td>✓</td>
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<tr>
<td>Pharmacokinetics</td>
<td></td>
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<tr>
<td>Half-life</td>
<td>11–16 h</td>
<td>15–60 h</td>
</tr>
<tr>
<td>Duration of action</td>
<td>6–15 h</td>
<td>4–8 h</td>
</tr>
<tr>
<td>Metabolic pathway</td>
<td>Phase II glucuronidation to levorphanol-3-glucuronide</td>
<td>3A4-, 2B6-, 2C19-mediated $N$-demethylation to EDDP</td>
</tr>
<tr>
<td>Opioid chemistry</td>
<td>Dehydroxylated phenanthrene</td>
<td>Diphenylheptane</td>
</tr>
<tr>
<td>Dosing</td>
<td>4 mg</td>
<td>7.5 mg</td>
</tr>
<tr>
<td>Suggested starting dose in opioid naïve patients</td>
<td>1 mg (1/2 x 2-mg tablet) PO 3 or 4 times daily (maximum daily starting dose, 4 mg); titrate up by up to 25% weekly, ie, if starting at 1 mg PO 4 times daily in the first week, increase to 1 mg PO 5 times daily at second week</td>
<td>2.5 mg (1/2 x 5-mg tablet) PO three times daily (maximum daily starting dose, 7.5 mg); titrate up by up to 25% weekly, ie, if starting at 2.5 mg PO 3 times daily first week, increase to 2.5 mg PO 4 or 5 times daily at second week (note: as the dose increases, percentage of upward titration decreases due to complex pharmacokinetics)</td>
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EDDP = 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidene; NE = norepinephrine; NMDA = N-methyl-D-aspartate.
unique pharmacokinetics of levorphanol, prescribers may consider with confidence a trial of this “forgotten opioid” in appropriate patients.

**Buprenorphine Patch**

The buprenorphine transdermal system (BTDS) was FDA approved in 2010 for the management of moderate to severe chronic pain in patients requiring a continuous, around-the-clock opioid analgesic for an extended time period. Injectable buprenorphine was approved in 1981 for acute pain, and in 2002 sublingual buprenorphine was approved for substance abuse treatment. BTDS was the first buprenorphine product approved in the United States for chronic pain; however, it has been available internationally since 2001. An international perspective is useful for aiding in understanding the relative potencies of the BTDS strengths available. In Europe, the BTDS dosage formulations available are 20 mg (35 μg/h), 30 mg (52.5 μg/h), and 40 mg (70 μg/h), requiring a patch change every 72 hours. The US-approved BTDS formulations are 5 mg (5 μg/h), 10 mg (10 μg/h), and 20 mg (20 μg/h), changed every 7 days. Of particular interest is that the highest available strength and delivery rate in the United States is equivalent to the lowest strength available in Europe.

Buprenorphine is a semisynthetic derivative of the naturally occurring opium alkaloid thebaine. Extensive first-pass metabolism (95%) made oral dosage formulations impractical, and therefore, prior to BTDS, the only available dosage formulations were injectable and sublingual (45%). Buprenorphine was available for years in Europe as a sublingual dosage formulation indicated for pain long before it was considered for the treatment of substance abuse. It is classified as a partial agonist/antagonist because it demonstrates partial agonism at the μ-opioid receptor, but with antagonist activity at δ- and κ-opioid receptors. Buprenorphine is highly lipophilic, with extensive distribution into tissues and passage across the blood–brain barrier. BTDS has a long half-life (up to 32 hours) and may require at least 21 hours to achieve therapeutic serum concentrations. Buprenorphine is metabolized into its active metabolite, N-dealkylbuprenorphine or norbuprenorphine, via oxidative CYP3A4 isozyme but has not been considered clinically relevant since the publication of drug-interaction studies employing ketoconazole.

The receptor-binding kinetics of buprenorphine are unique. Buprenorphine has high affinity for the μ-opioid receptor but associates (30 minutes) and dissociates slowly (166 minutes) and incompletely (50%) from opioid receptors. Analgesia is achievable with 5% to 10% saturation at μ-opioid receptors, but the minimum effective concentration for analgesia is 100 pg/mL, which in pharmacokinetic studies was achievable with BTDS 10 μg/h (Figure 2). Receptor saturation is particularly important with buprenorphine because its high affinity and robust binding

![Figure 2. Plasma buprenorphine concentrations with the administration of buprenorphine 10 μg/h once weekly for 3 weeks (N = 36).](image-url)
capacity make displacement by other opioids, including naloxone, difficult or impossible. For example, 2 ng/mL of buprenorphine can displace an equal concentration of fentanyl from 90% opioid receptors, yet compared with fentanyl, it requires 40 times the amount of naloxone to reverse buprenorphine. To block the effects of heroin or other opioid use, complete receptor saturation is the goal for products intended to treat substance abuse, such as buprenorphine hydrochloride or buprenorphine/naloxone. A 16-mg dose of buprenorphine/naloxone occupies 79% to 95% of available opioid receptors and a 32-mg dose of buprenorphine/naloxone is capable of blocking the effects of 120 mg of morphine for >29.5 hours. These properties are believed to result in reduced addiction potential, with less euphoria at onset and fewer withdrawal effects on discontinuation. BTDS was approved based on 3 pivotal Phase III randomized, double-blind trials in patients with chronic low back pain (2 trials) and osteoarthritis (1 trial). In the first study, opioid-naive patients were enrolled for a run-in period in which tolerability of BTDS was determined (patients were randomized to receive BTDS, initiated at 5 µg/h for 3 days and increased to 10 µg/h, or placebo); patients were discontinued before randomization if BTDS was poorly tolerated. After 12 weeks of treatment, the primary end point, average pain over the previous 24 hours as measured on a 10-point VAS, was significantly improved compared with placebo (P < 0.01). In the second study, opioid-experienced patients were also enrolled in a run-in period to evaluate tolerability of a 20-µg/h dose, after initiation on 10 µg/h, and were discontinued if unable to tolerate; patients were otherwise randomized to BTDS 20 µg/h, immediate-release (IR) oxycodone 40 mg/d, or BTDS 5 µg/h (utilized as an active-control group). After 12 weeks, the primary end point (average pain over the previous 24 hours as measured on a 10-point VAS) was significantly improved with BTDS 20 µg/h and oxycodone IR 40 mg/d compared with BTDS 5 µg/h (both, P < 0.001); the difference between BTDS 20 µg/h and oxycodone IR 40 mg/d was not significant. The third trial compared BTDS to sublingual buprenorphine in patients with hip or knee osteoarthritis over 7 days. Although both groups showed a nearly 50% reduction in pain scores, the BTDS group demonstrated a more favorable AE profile.

The AE profiles of opioids are generally problematic in elderly patients, who are particularly sensitive to common AEs. Buprenorphine is believed to have an increased safety profile compared with other opioids, and BTDS in particular has been associated with decreased nausea, vomiting, and constipation at least in part as a result of transdermal delivery, which avoids direct contact with GI opioid receptors and linear serum concentrations that avoid peak and trough kinetic profiles. Unlike with other opioids, buprenorphine-induced respiratory depression has a ceiling effect at low therapeutic concentrations, resulting in increased tolerability. In a postmarketing surveillance study published in Europe, 13,179 patients were enrolled for moderate to severe pain after failing previous opioid therapy or experiencing intolerable AEs. One half of the patients were aged >70 years, but age did not affect efficacy, as 80% of patients reported either very good or good pain relief, and an additional 9% reported satisfactory. In addition, every patient was started on the 37.5-µg/h dose, and only 18% of patients required an increased dose. At the end of the study, 70% of patients elected to continue therapy with BTDS. The most common AEs were nausea (4%), dizziness (1.9%), vomiting (1.6%), and constipation (1%). Adverse reactions from Phase III clinical trials in the United States were similarly low, with application-site reactions to the patch occurring most frequently in roughly 17% of patients to as much as 29% with the highest dose (20 µg/mL). In the opioid-naive trial, AEs occurring at rates higher than that with placebo (Treatment group – Placebo group) included constipation (3%), dizziness (3%), nausea (2%), and vomiting (2%). The opioid-experienced trial demonstrated that many of the AEs are dose dependent (BTDS 20 mg – BTDS 5 mg)—nausea (4%), vomiting (3%), constipation (3%), dizziness (3%), somnolence (3%), and headache (6%). The Initiation and Titration Guide provided by the manufacturer may be confusing to providers attempting a patient trial of BTDS because it utilizes morphine-equivalent (MEQ) conversions that are conservative, reports atypical equianalgesic dose conversions of common opioids, and does not reflect evidence-based potencies for buprenorphine. Although equianalgesic opioid dose conversion is admittedly inconsistent, and the manufacturer cautiously provides equivalencies, listing hydrocodone as having twice the potency compared with generally accepted morphine conversions is conservative to the point of duplicity (Table III). Codeine and oxycodone conversions are...
debatable, but hydrocodone is generally accepted as equivalent to morphine or, in some sources, slightly less potent.\textsuperscript{92–98} The conversions from the guide were also utilized in the Phase III trial in opioid-experienced patients.\textsuperscript{84} This simple conversion has a significant impact on the study, as 62\% of the patients enrolled were on stable doses of hydrocodone prior to the study. Utilizing their conversion, the mean MEQ prior to enrollment (51.6 mg) corresponds to hydrocodone 25.8 mg, which, according to their titration guide, should be a 5-\textmu{}g/h patch, but patients unable to tolerate 20 \textmu{}g/h were discontinued from the study. The recommended MEQs seem to favor the 5-\textmu{}g/h patch, which was not studied except as an ineffective control, whereas the 20-\textmu{}g/h patch, the focus of the opioid-experienced trial, appears in the guide to be unavailable or contraindicated based on the MEQ conversions. Also, converting hydrocodone 25.8 mg MEQ to oxycodone 17.2 mg (20:30) or 12.9 mg (15:30), depending on acceptable conversion ratios, represents 2.3 to 3.1 times the daily dose utilized by patients prior to the study. Such a large increase would not be advisable in clinical practice, and it therefore is no surprise that the oxycodone group had favorable results.

Moreover, in light of the previous discussion, careful analysis and consideration are particularly imperative for any opioid from any manufacturer where conversion estimates are conservative, especially if one uses an opioid conversion calculator. Conversion calculators generally use fixed mathematic conversion equations; therefore, a conservative dose estimate in one direction is liberal in the opposite direction.\textsuperscript{101}

BTDS is an ideal dosage formulation for elderly patients with chronic pain due to a better safety profile, improved compliance with 7-day wear time, and low addiction potential, as reflected by its status as a schedule III opioid, which affords up to 5 refills. BTDS demonstrated efficacy in osteoarthritis and low back pain, which are the 2 most common pain conditions reported in the elderly. For all of these reasons, BTDS is an attractive option for stable elderly patients.

### Tapentadol

Tapentadol is an opioid that possesses unique pharmacology and certain attributes that make it particularly useful in the elderly. Tapentadol is available as an IR tablet or solution, and was FDA approved in 2009 for the management of moderate to severe acute pain.\textsuperscript{102} An extended-release (ER) tablet was approved in 2011 for the management of moderate to severe chronic pain and later gained approval

<table>
<thead>
<tr>
<th>Drug</th>
<th>5 \textmu{}g/h ((&lt;30 \text{ mg}))</th>
<th>10 \textmu{}g/h (30–80 \text{ mg})</th>
<th>20 \textmu{}g/h ((&gt;80 \text{ mg})*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocodone</td>
<td>(&lt; 15)</td>
<td>15–40</td>
<td>(&gt; 40^*)</td>
</tr>
<tr>
<td>Oxycodeone</td>
<td>(&lt; 15)</td>
<td>15–40</td>
<td>(&gt; 40^*)</td>
</tr>
<tr>
<td>Tramadol</td>
<td>(&lt; 300)</td>
<td>300–400</td>
<td>(&gt; 250^*)</td>
</tr>
<tr>
<td>Codeine</td>
<td>(&lt; 90)</td>
<td>90–250</td>
<td>(&gt; 530)</td>
</tr>
</tbody>
</table>

*EB = evidence-based; MEQ = morphine equivalent. *Per guide, buprenorphine may not be appropriate.

<table>
<thead>
<tr>
<th>Drug</th>
<th>1:75 \textsuperscript{99,100}</th>
<th>1:110 \textsuperscript{99,100}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocodone</td>
<td>9</td>
<td>13.2</td>
</tr>
<tr>
<td>Oxycodeone</td>
<td>18</td>
<td>26.4</td>
</tr>
<tr>
<td>Tramadol</td>
<td>36</td>
<td>52.8</td>
</tr>
</tbody>
</table>

EB = evidence-based; MEQ = morphine equivalent.

*Per guide, buprenorphine may not be appropriate.
specifically for diabetic neuropathy requiring continuous, around-the-clock opioid analgesic for an extended period of time. Shortly after tapentadol approval in the United States, the drug was approved in the European Union. The focus of Phase III trials was conditions common in elderly patients, including hip or knee osteoarthritis, chronic low back pain, and diabetic peripheral neuropathy. In fact, tapentadol is the only opioid currently FDA approved for use in patients with neuropathic pain. Tapentadol IR is available in various strengths (50, 75, 100 mg) scheduled every 4 to 6 hours, and ER available strengths (50, 100, 150, 200, 250 mg) are scheduled twice daily. ER formulations were found to be bioequivalent to IR, resulting in a simple 1:1 conversion and allowing for easy dose conversions. However, the maximum daily dose of the ER formulation is 500 mg per 24 hours, unlike that of the IR formulation, which is 600 mg per 24 hours, other than the first day of therapy, which allows for 700 mg to provide an analgesic loading dose.

The research effort into mechanisms of pain relief during the 1990s, mentioned previously, focused on research into the influence of centrally mediated monoaminergic transmission and its influence on chronic and neuropathic pain. Clinical evidence has demonstrated that increasing extracellular concentrations of 5-HT and NE in descending pain inhibitory pathways exerts an analgesic effect. NE is the monoamine primarily involved in attenuating pain signals and is particularly useful in neuropathic pain. As a result, serotonin–norepinephrine reuptake inhibitors (venlafaxine, duloxetine, milnacipran) and dopamine–norepinephrine reuptake inhibitors (bupropion) have largely replaced tricyclic antidepressants in the treatment of neuropathies, particularly in the elderly, due to significant anticholinergic activity, which places them on the Beers list. Important detriments of tricyclic antidepressants include sedation, QTc prolongation, and anticholinergic effects (xerophthalmia, xerostomia, urinary retention, constipation).

Polypharmacy is a significant concern in the elderly population, in which the average number of medications often exceeds 10, resulting in a higher prevalence of drug interactions, duplication of therapy, and lack of compliance. However, in pain management, rational polypharmacy or utilizing multiple medications with variable pharmacologic mechanisms at low doses may offer analgesic efficacy while minimizing AEs. Clinically, it appears that combining an opioid agonist with a monoamine reuptake inhibitor has an opioid-sparing effect that would be expected to increase pain relief and minimize AEs.

Ideally, a single medication capable of combining both mechanisms could be identified, and the first product of pharmacologic research into this possibility was tramadol. Tapentadol and tramadol are the currently approved agents combining μ-opioid agonism and monoamine reuptake inhibition, so comparisons are inevitable (Table IV). Tapentadol was intentionally designed to overcome tramadol’s barriers to efficacy. Racemic tramadol possesses both NE and 5-HT reuptake inhibition combined with insignificant affinity for opioid receptors (6000 times less than morphine) but is highly dependent on metabolic activation for increased potency at opioid receptors. O-desmethyl-tramadol (M-1), the major analgesic metabolite, has 200-fold greater affinity for μ-opioid receptors and results in 6 times more analgesia than racemic tramadol. Unfortunately, M-1 requires CYP2D6 metabolism for activation, which 5% to

<table>
<thead>
<tr>
<th>Properties</th>
<th>Tramadol</th>
<th>Tapentadol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mu binding affinity</td>
<td>6000× less than morphine</td>
<td>18× less than morphine</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Significant CYP</td>
<td>Conjugation, O-glucuronide</td>
</tr>
<tr>
<td>Drug interactions</td>
<td>See above</td>
<td>See above</td>
</tr>
<tr>
<td>Neuroamine activity</td>
<td>5-HT/NE</td>
<td>NE, almost no 5-HT</td>
</tr>
</tbody>
</table>

5-HT = serotonin; CYP = cytochrome P450; NE = norepinephrine.
Table V. Adverse-events profiles of tapentadol and oxycodone in Phase III clinical trials. Values are percentages of patients.

<table>
<thead>
<tr>
<th>Study</th>
<th>GI</th>
<th>CNS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nausea</td>
<td>Vomiting</td>
</tr>
<tr>
<td></td>
<td>Tapentadol</td>
<td>Oxycodone</td>
</tr>
<tr>
<td>IR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hartrick et al&lt;sup&gt;119&lt;/sup&gt; (end-stage joint disease)</td>
<td>18</td>
<td>41</td>
</tr>
<tr>
<td>Daniels et al&lt;sup&gt;120&lt;/sup&gt; (post-bunionectomy)</td>
<td>49</td>
<td>67</td>
</tr>
<tr>
<td>Hale et al&lt;sup&gt;121&lt;/sup&gt; (LBP and OA)</td>
<td>18</td>
<td>29</td>
</tr>
<tr>
<td>ER</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buynak et al&lt;sup&gt;122&lt;/sup&gt; (LBP)</td>
<td>20</td>
<td>35</td>
</tr>
<tr>
<td>Afrilalo et al&lt;sup&gt;123&lt;/sup&gt; (knee OA)</td>
<td>22</td>
<td>37</td>
</tr>
<tr>
<td>Schwartz et al&lt;sup&gt;124&lt;/sup&gt; (DPN)</td>
<td>14</td>
<td>—</td>
</tr>
<tr>
<td>Wild et al&lt;sup&gt;125&lt;/sup&gt; (LBP and OA, LT safety and efficacy)</td>
<td>18</td>
<td>33</td>
</tr>
</tbody>
</table>

CNS = central nervous system; DPN = diabetic peripheral neuropathy; GI = gastrointestinal; IR = immediate release; LBP = low back pain; LT = Long-term; OA = osteoarthritis; ER = extended release.

*CNS side effects.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism in Pain</th>
<th>Efficacy</th>
<th>Metabolism</th>
<th>Advantages</th>
<th>Special Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buprenorphine</td>
<td>μ-Opioid agonist, κ-opioid antagonist</td>
<td>General pain syndromes</td>
<td>N-dealkylation to norbuprenorphine via CYP3A4 (slightly active); glucuronidation of both metabolite and parent compound</td>
<td>Prevents withdrawal symptoms; easy compliance (1 patch/wk); antidepressive/antianxiety effects</td>
<td>May take up to 72 h to reach steady state</td>
</tr>
<tr>
<td>Diclofenac patch</td>
<td>Anti-inflammatory</td>
<td>Musculoskeletal, somatic pain</td>
<td>Sulfate and glucuronidate conjugates of metabolites and eliminated through urinary and biliary excretion</td>
<td>Localized nonsteroidal activity; very little systemic absorption; found effective for sprains, strains, contusions, knee OA, epicondylitis</td>
<td>Oral NSAIDs limited in elderly due to possible complications of GI bleed, nephrotoxicity, cardiovascular events</td>
</tr>
<tr>
<td>Levorphanol</td>
<td>μ-Opioid agonist; κ-opioid agonist; NMDA antagonist; NE reuptake inhibitor</td>
<td>Neuropathic pain and general pain syndromes</td>
<td>Glucuronidation to levorphanol-3-glucuronide (inactive)</td>
<td>Treatment of neuropathic pain; additional analgesic benefits via-κ-opioid agonist; no QTc prolongation; alternative to methadone; no DI with CYP340 system</td>
<td>Long half-life (~15 h); slow titration; only 2-mg oral dose available</td>
</tr>
<tr>
<td>Methadone</td>
<td>μ-Opioid agonist; NMDA antagonist; NE reuptake inhibitor</td>
<td>Neuropathic pain and general pain syndromes</td>
<td>Major: N-demethylation to EDDP (inactive) via CYP3A4, -2B6, -2C19</td>
<td>Treatment of neuropathic pain; multiple forms available; (IV/IM/oral solution)</td>
<td>Can cause QTc prolongation; multiple drug interactions (including P-gp substrate and 3A4 inducer); variable/long half-life (8–59 h); high volume of distribution; slow titration</td>
</tr>
</tbody>
</table>

(continued)
<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism in Pain</th>
<th>Efficacy</th>
<th>Metabolism</th>
<th>Advantages</th>
<th>Special Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tapentadol</td>
<td>( \mu )-Opioid agonist; NE reuptake</td>
<td>Neuropathic pain</td>
<td>Major: glucuronidation to O-glucuronide;</td>
<td>No major drug interactions; no active metabolites; less GI upset</td>
<td>May be expensive</td>
</tr>
<tr>
<td></td>
<td>inhibitor</td>
<td></td>
<td>minor: methylation to ( N )-desmethyl-</td>
<td>(compared to oxycodone); no risk of serotonin syndrome; no QTc prolongation</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>tapentadol via 2C9/2C19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tramadol</td>
<td>( \mu )-Opioid agonist; NE reuptake</td>
<td>Neuropathic pain</td>
<td>O-demethylated metabolite via CYP2D6 (active); 10 other metabolites (inactive)</td>
<td>Alternative to opioid intolerant patients; affects mood via 5-HT reuptake inhibitor</td>
<td>6000( \times ) less potent than morphine; Risk of serotonin syndrome/seizure; Prodrug requires activation; 5%-15% of white population are “poor metabolizers” due to 2D6 metabolism</td>
</tr>
</tbody>
</table>

5-HT = serotonin; CYP = cytochrome P-450; DI = drug interactions; EDDP = 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidene; GI = gastrointestinal; NE = norepinephrine; NMDA = \( N \)-methyl-\( \alpha \)-aspartate; OA = osteoarthritis; P-gp = P-glycoprotein.
15% of the white population lacks, and can be antagonized by 2D6 inhibitors, including specific serotonin reuptake inhibitors, quinidine, and amitriptyline, preventing effective analgesia.\textsuperscript{116,117} Finally, the potential risk for serotonin syndrome when combining tramadol’s serotonergic reuptake inhibition with other agents that increase serotonin may limit its clinical utility.\textsuperscript{118}

In contrast, comparing tapentadol to morphine, binding assays demonstrated that tapentadol has 18 times less affinity for \( \mu \)-opioid receptors, but functional analgesia was 2 to 3 times less potent in animal studies.\textsuperscript{106} In Phase III clinical trials, tapentadol was compared to oxycodone and was determined to be 5 times less potent (50 mg tapentadol equivalent to 10 mg oxycodone and 100 mg tapentadol equivalent to 20 mg oxycodone), supporting the increased potency observed in animal trials.\textsuperscript{119–125} The combined synergy of \( \mu \)-opioid receptor agonism with NE reuptake inhibition was further confirmed in animal models because naloxone and yohimbine, a potent \( \alpha_2 \)-adrenergic antagonist, both demonstrated only partial inhibition of tapentadol in pain models.\textsuperscript{106} Another advantage to the dual mechanism of action of tapentadol is the delayed development of tolerance compared with that of morphine; tolerance to morphine developed 2.5 times faster than did that to tapentadol.\textsuperscript{106}

Tapentadol has no active metabolites, and all analgesic properties are retained in the nonracemic parent compound. Tapentadol undergoes hepatic metabolism via phase II conjugation, with 13% as CYP substrates that are not considered clinically relevant.\textsuperscript{126} Tapentadol selectively inhibits NE reuptake, with an affinity and potency comparable to those of venlafaxine, thereby increasing efficacy while avoiding the potential risk for serotonin syndrome.\textsuperscript{106} In pharmacokinetic studies, maximum serum concentrations of tapentadol were 2.5-fold higher in 3 patients with moderate hepatic impairment (Child-Pugh score \( \geq 9 \)) than in healthy subjects.\textsuperscript{127} Dose adjustment may be required for moderate to severe hepatic impairment and can be achieved by increasing the dosing interval to every 8 hours, starting at lower doses, and with cautious dose increases. Tapentadol has a low risk for drug interactions and does not depend on metabolic activation for efficacy, and its dual mechanism of action results in reduced AE profile compared with those of other opioids.

A reduced AE profile affords the elderly population a significant advantage because their sensitivity to the AEs associated with conventional opioids often leads to intolerance, lack of compliance, and treatment failure.\textsuperscript{7} The elderly population was well represented in Phase III clinical trials of tapentadol ER, with nearly 25% of overall participants aged \( \geq 65 \) years.\textsuperscript{122–125} GI AEs (nausea, vomiting, constipation) are the most common overall AEs associated with opioid use, and those associated with the use of tapentadol are consistently close to half (Table V\textsuperscript{121–127}) of those reported with oxycodone.\textsuperscript{128} The CNS effects (dizziness, somnolence, headache) of tapentadol are comparable to those of oxycodone and should be monitored to avoid an increased risk for falls. Overall, tapentadol represents a therapeutic advantage over other opioids in the elderly population due to its unique mechanism of action, low potential for drug interactions, and significantly reduced AE profile.

**DISCUSSION**

Further studies are needed to validate analgesic outcomes for topical versus oral NSAIDs in the elderly in terms of both safety and efficacy; methadone versus levorphanol to further validate safety particularly due to methadone CYP450 or P-glycoprotein interactions. While we have data on tapentadol and buprenorphine in the elderly, each measured against oxycodone alone, it would be helpful to have larger trials using “summed pain intensity difference” (SPID) for each of these agents against more commonly used opioids such as oxycodone IR, hydrocodone IR, tramadol, and other opioids.

We have identified the rationale, various pitfalls and opportunities that exist for currently available analgesic therapies which could be particularly advantageous in the elderly patient, but that are often overlooked. Interestingly, although we focused the discussions on certain therapies, they range from very old drugs, to very new drugs with varying pharmaceutical delivery options. Finally, we present a summary in Table VI for consideration when contemplating these unique therapeutic options for the elderly patient.

**CONCLUSIONS**

It is incumbent that providers consider DETP, levorphanol, BTDS, and tapentadol as part of an analgesic armamentarium in an effort to maximize therapeutic
benefit and to minimize risks in the increasing elderly patient population. Moreover, providers must continue to assess various contemporary medication options for this population as new drugs and dosage formulations become available.

ACKNOWLEDGMENTS
Dr. Atkinson was the primary researcher and author for all sections of the paper including figures and tables and coordinated the activities of all other participants. Dr. Fudin was the subject matter expert who selected agents to research, primary editor, author of paragraphs in introduction and conclusion, and creator of levorphanol table. Dr. Pandula researched and developed physiologic changes in elderly, introduction adapted from her work, and creator of the table for physiologic changes in the elderly. Ms. Mirza contributed to the tapentadol section, created the final summary table, and worked on formatting all tables for consistency.

CONFLICTS OF INTEREST
This commentary is the sole opinion of the authors and does not reflect the opinion of employers, employee affiliates, and/or pharmaceutical companies mentioned or specific drugs discussed. It was not prepared as part of the official government duties of Drs. Atkinson, Fudin, or Pandula as clinicians.

Dr. Fudin is a member of the speakers’ bureau at Cadence Pharmaceuticals, Cumberland Pharmaceuticals, Janssen Pharmaceuticals, Millennium Laboratories, and Purdue Pharma. He is a consultant to Practical Pain Management in the development of an Online Opioid Calculator. He provides expert testimony but has no pending cases involving any of the drugs discussed.

The authors have indicated that they have no other conflicts of interest with regard to the content of this article.

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