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Alternative methods of pain management for the older adult population: Review of topical pain medications

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Abstract

The older adult population is one of the fastest growing age groups in the United States. As this population continues to expand, determining the safest way to provide pain management has become increasingly important. More than 50% of community-dwelling older adults experience pain on a daily basis, and up to 83% of those in assisted living facilities experience persistent pain. Pain is exceedingly challenging to treat safely and effectively in the elderly because of the physiologic changes that occur as people age. In addition, many nonnarcotic medications with analgesic properties are listed in both the 2012 American Geriatrics Society Beers Criteria for Potentially Inappropriate Medication Use in Older Adults and the Pharmacy Quality Alliance high-risk medications lists. An approach to the growing challenge of managing pain in the elderly that is gaining popularity among community-dwelling patients is the use of topical pain medications. The goal of this article is to review some of the available literature regarding the use of various topical analgesics alone or in combination, and to discuss their known or theoretical mechanisms of peripheral pain modulation. Commercially available or compounded topical pain medications may be used to replace or augment doses of oral medications in an effort to decrease the risk of adverse drug events for older adult patients. When prescribing topical pain medications physicians should consider the nature of the pain targeted, the type of analgesia expected from each ingredient, the potential for systemic absorption, and related side effects.

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Introduction

The older adult population is one of the fastest growing age groups in the United States, and determining the safest way to provide pain management for older adults has become increasingly important. Common pain syndromes among the elderly include osteoarthritis, neuropathies (eg, diabetic, atherosclerotic, postherpetic), chronic lower back pain, fibromyalgia, injury sustained from falls with or without fracture, and cancer pain.[1] More than 50% of community-dwelling older adults are estimated to experience pain on a daily basis, and up to 83% of those in assisted living facilities experience persistent pain.[2,3] However, a considerable percentage of this population continues to experience untreated or undertreated pain. Selecting the appropriate pain management strategy for older adult patients raises many challenges, including concerns regarding pharmacokinetic changes and resulting changes in drug safety.

Many pharmacokinetic and pharmacodynamic changes that take place during the natural aging process affect medication selection. Total body water decreases, which changes the distribution of hydrophilic medications. Gastric motility decreases, which affects the time to peak serum concentrations of medications. Renal clearance and hepatic metabolic enzyme activity decrease, which may lead to reduced drug metabolism and elimination.[4] With reduced drug elimination there is an increased risk of adverse drug events because of prolonged exposure and possible accumulation of medications and their metabolites. When coupled with age-related decline in mobility and balance, and an increased sensitivity to the central nervous system (CNS) effects of many medications, dangerous outcomes are possible even with small doses of potentially inappropriate or high-risk medications.

It is well known that nonsteroidal anti-inflammatory drugs (NSAIDs) are not safe for chronic use in the elderly because of the risk of gastrointestinal bleeding (GI), peptic ulceration, nephrotoxicity, cardiovascular events, and heart failure exacerbation. In addition, many nonnarcotic medications with analgesic properties are listed in both the 2012 American Geriatrics Society Beers Criteria for Potentially Inappropriate Medication Use in Older Adults and the Pharmacy Quality Alliance (PQA) high-risk medication lists.[5] The PQA high-risk medication list is connected to the Centers for Medicare & Medicaid Services star measures, which are used to rate the quality of care provided by Medicare Advantage Plans and determine their bonus payments.[6]

Interestingly, opioid analgesics, with the exception of meperidine, do not appear on either list. In 2012 the American Geriatrics Society released a statement on the use of opioids in the treatment of persistent pain in older adults that noted opioids can be used effectively and safely to treat persistent pain if adequately monitored.[7] Multiple clinical practice guidelines suggest opioid analgesics may be safe and effective for carefully selected older adult patients with no history of abuse, diversion, or addiction. [8] However, some prescribers and older adult patients continue to have an aversion to the use of opioid analgesics. This aversion is often attributed to a general fear of opioids, addiction, or risk of opioid-induced side effects. Opioid-related adverse events of particular concern in older adult patients include constipation, falls, fractures, and delirium.[9,10] Opioid-induced constipation may be effectively managed with prophylactic bowel regimens. Data suggesting increased risks of delirium, falls, and fractures are of questionable quality because of baseline variability in patient history of falls and health status, but these data may continue to dissuade prescribers and patients from using opioids for moderate to severe pain.[10-12]

In light of the dangers of NSAIDs and the aversion many have to opioid analgesics, the use of topical pain medications is gaining popularity among community-dwelling older adult patients. The 2012 recommendations for use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee conditionally recommend that persons 75 years and older use topical NSAIDs rather than oral NSAIDs.[13] As such, the appearance of commercially available topical medications and compounded products has become increasingly common in the medication profiles of community-dwelling patients.

One key benefit of prescribing a topical analgesic is an increase in local tissue concentration without significant systemic absorption. This can drastically reduce or eliminate the risk of centrally mediated side effects, systemic adverse events, and drug-drug interactions. Additional benefits include avoidance of the effects of first-pass metabolism, prevention of GI irritation, interactions with gastric content, and reduction of gastric motility. The avoidance of both central and peripheral side effects (not including dermatologic reactions) makes this route of administration ideal for the aging population.

Some limitations to the use of topical medications include variations in skin and tissue penetration between individuals and application sites, the potential for application site reactions, and limitations in skin permeability based on particle size and physicochemical properties.[14] It is suggested that particles have a molecular mass less than 500 Da for optimal skin penetration.[15] A balance of lipophilicity and hydrophilicity is required for particles to pass the stratum corneum and epidermis. Vehicle pH and level of occlusion may also affect particle diffusion.[15] Additionally, topically applied medications must have a peripheral site mechanism of action to produce a clinical benefit.

To better understand the proper use of topical medications for pain control, it is important to note the distinction between topical and transdermal administration. Topical medications are applied directly to the skin in a specified area with the goal of producing a local action on the surface of the skin or underlying soft tissue. Transdermal medications are applied to the skin with a goal of achieving enough absorption to produce a desired systemic effect. Although topical medications must be applied to the affected area, transdermal medications may be applied to any suitable area based on tissue composition and skin integrity. Most topical medications are supplied as a cream, gel, or ointment depending on the desired action, drug bioavailability, and stability.[16] However, transdermal medications are often supplied via a delivery system or patch that is designed to allow the drug to diffuse through intact skin and into the systemic circulation. It is important to remember some creams, gels, and pastes may produce significant systemic absorption based on drug particle size and vehicle selection (eg, nitroglycerin ointment, oxybutynin gel). Potential systemic absorption must be considered when determining the appropriate combination of ingredients for an analgesic compound.

This article reviews the literature to support the use of various topical analgesics alone or in combination with a focus on known or theoretical mechanisms of peripheral pain modulation. The article will also examine some relevant cost considerations.

Capsaicin

Capsaicin is a very lipophilic exogenous vanilloid receptor agonist that works in the skin. When applied, topical

capsaicin causes the TRPV1 (transient receptor potential vanilloid 1) channel to open, allowing for an influx of calcium into nociceptive sensory nerve fibers, leading to high levels of intracellular calcium with resulting enzymatic, cytoskeletal, and osmatic changes.[17] In addition, at high concentrations capsaicin directly inhibits mitochondrial respiration, leading to nerve terminal retraction from the epidermis and dermis. Both mechanisms lead to extended periods of impaired local nociceptor function.[17]

A 2013 Cochrane review found that high-concentration topical capsaicin (8% patch) was more effective than lower concentration capsaicin for the treatment of neuropathic pain, leading to improvements in sleep, depression, and quality of life. The authors suggest that high-concentration capsaicin has an efficacy similar to other therapies for chronic neuropathic pain, such as oral gabapentin and pregabalin. Despite the reported efficacy, the authors recommend high-concentration capsaicin be reserved for the management of pain that has failed these other available therapies, because of the high cost of application.[18]

A 2012 Cochrane review evaluated the efficacy of low-concentration (<1%) capsaicin cream for neuropathic pain. The authors found 6 studies with small numbers of participants and variable definitions of efficacy. Two articles reported data on ≥50% pain reduction, but because of small numbers, no statistical analysis could be performed. The authors concluded there was insufficient evidence to support the use of low-concentration topical capsaicin cream over placebo for the management of neuropathic pain, and they noted the prevalence of local skin irritation, which is often mild and transient but may lead to withdrawal.[19]

With regard to nonneuropathic pain syndromes, studies have demonstrated moderate effectiveness of low-concentration topical capsaicin products in the management of chronic soft tissue pain, osteoarthritis, and low back pain. Capsaicin 0.05% cream was found to cause a 49% decrease in mean pain sum score in patients with chronic soft tissue pain.[20] A meta-analysis on topical capsaicin (0.025%-0.057%) for osteoarthritis cited disagreement on effectiveness among included articles. The authors ultimately concluded that four times daily topical capsaicin is moderately effective at reducing pain intensity up to 20 weeks.[21] Please see Table 1 for a summary of topical capsaicin clinical trial data.

Nonsteroidal Anti-Inflammatory Drugs

Topical NSAIDs produce a secondary analgesic effect by reducing inflammation at the site of pain/injury, and can therefore only produce significant analgesia if there is an inflammatory component to the targeted pain. Topical NSAIDs inhibit the activity of cyclooxygenase to block the formation of prostaglandins, which promote the infiltration of inflammatory cells and stimulate inflammation-associated hyperalgesia.[34,35] Multiple NSAIDs have been studied for topical administration, including ketoprofen, ibuprofen, and diclofenac. Good pain relief has been reported with the use of topical NSAIDs for acute musculoskeletal pain conditions and chronic rheumatologic conditions.[36] Studies also demonstrate an improved safety profile for topical NSAIDs, with rare reports of GI adverse events compared with the 15% incidence reported with oral NSAIDs.[37] One review of 194 adverse reactions attributed to topical NSAIDs (ketoprofen, piroxicam, diclofenac, naproxen, and indomethacin) found that 95% of adverse reactions were dermatologic in nature. All systemic reactions evaluated in this study involved ketoprofen or piroxicam and could be characterized as GI or allergic (eg, dyspnea, angioedema).[38] A separate case-control study involving 1103 patients hospitalized for upper GI bleed or perforation found that topical NSAIDs were not significantly associated with an increased risk of GI bleed or perforation after adjustment for concomitant use of oral NSAIDs and ulcer-healing medications.[39] This highlights the increased risk of GI adverse events associated with concomitant use of topical NSAIDs and oral NSAIDs. If a patient is initiated on a topical NSAID, consider discontinuing routinely prescribed oral NSAIDs to reduce the risk of adverse effects.

Note that topical NSAIDs are not included in the Beers Criteria.[5] In the United States, commercially available topical diclofenac preparations have the same product box warning for cardiovascular risk and GI risk that is attached to oral NSAIDs, but single- and multiple-dose absorption studies demonstrate peak plasma levels of less than 10% of those observed after oral NSAID administration (ranging from 0.2% to 8.0%). This may lead to a significantly lower risk of systemic adverse effects.[40] Indirect comparisons of topical NSAIDs indicate ketoprofen provides superior analgesia to ibuprofen, piroxicam, and indomethacin, the last of which provided the lowest evidence of benefit.[41] Please see Table 2 for a summary of topical NSAID clinical trial data.

Lidocaine

Lidocaine is a local anesthetic that produces analgesia when applied topically. Topical lidocaine is believed to act on sensitized and hyperactive cutaneous nociceptors by blocking voltage-gated sodium channels to silence ectopic impulses without causing complete afferent conduction blockade.[15,46,47] Recent studies have also demonstrated that topical lidocaine produces significant pain relief in skin where there has been marked nociceptor impairment or complete loss.[47] Pharmacokinetic studies suggest very minimal systemic absorption from lidocaine patches after

TABLE 1: Topical capsaicin clinical trials

Study	Study characteristics	Treatment arms	Results
HIV neuropathy			
Clifford et al,[22] 2012	Design: R, PC, DB, parallel groups, single app	Capsaicin 8% patch 30 min	Capsaicin 8% > capsaicin 0.04%
	N = 494	Capsaicin 8% patch 60 min	≥30% pain reduction from baseline
	Duration: 12 wk	Capsaicin 0.04% patch 30 min	
		Capsaicin 0.04% patch 60 min	
Simpson et al,[23] 2008	Design: R, PC, DB, multicenter, parallel groups, single app	Capsaicin 8% patch 30 min	Capsaicin 8% > capsaicin 0.04%
	N = 307	Capsaicin 8% patch 60 min	≥30% pain reduction from baseline
	Duration: 12 wk	Capsaicin 8% patch 90 min	
		Capsaicin 0.04% patch	
Postherpetic neuralgia			
Backonja et al,[24] 2008	Design: R, PC, DB, multicenter, parallel groups, single app	Capsaicin 8% patch 60 min	Capsaicin 8% > capsaicin 0.04%
	N = 402	Capsaicin 0.04% patch 60 min	≥30% pain reduction from baseline
	Duration: 12 wk		
Irving et al,[25] 2010	Design: R , PC, DB, multicenter, parallel groups, single app	Capsaicin 8% patch 60 min	Capsaicin 8% > capsaicin 0.04%
	N = 416	Capsaicin 0.04% patch	≥50% pain reduction from baseline
	Duration: 12 wk		≥30% pain reduction from baseline
Bernstein et al,[26] 1989	Design: R, PC, DB, parallel study	Capsaicin 0.075% 3-4 times daily	Capsaicin > placebo
	N = 32	Vehicle	≥40% pain reduction from baseline
	Duration: 6 wk		
Watson et al,[27] 1993	Design: R, PC, DB, parallel study	Capsaicin 0.075% 4 times daily	Capsaicin > placebo
	N = 143	Vehicle	Reduction in pain
	Duration: 6 wk		
Diabetic peripheral neuropathy			
Kulkantrakorn et al,[28] 2013	Design: R, PC, DB, crossover	Capsaicin 0.025% 3-4 times daily	Capsaicin = placebo
	N = 33	Vehicle	
	Duration: 8 wk		
Osteoarthritis			
Altman et al,[29] 1994	Design: R, PC, DB	Capsaicin 0.025% 4 times daily	Capsaicin > placebo
	Multicenter study	Vehicle	Reduction in pain
	N = 113		Reduction in pain on passive range of motion
	Duration: 12 wk		Joint tenderness
McCarthy and McCarty,[30] 1992	Design: R, PC, DB	Capsaicin 0.075% 4 times a day	Capsaicin > placebo
	N = 14	placebo	Reduction in pain, reduction in tenderness
	Duration: 4 wk		
Deal et al,[31] 1991	Design: R, PC, DB	Capsaicin 0.025% 4 times a day	Capsaicin > placebo
	N = 70	Placebo	Reduction in pain
	Duration: 4 wk		

TABLE 1: Topical capsaicin clinical trials (continued)

Study	Study characteristics	Treatment arms	Results
Schnitzer et al,[32] 2012	Design: multicenter, RT, DB N = 695 Duration: 12 wk	Civamide 0.075% Civamide 0.01%	Civamide 0.075% > civamide 0.01%. Reduction in pain, improvement in physical function
Kosuwon et al,[33] 2010	Design: R, PC, DB, crossover N = 99 Duration: 4 wk	Capsaicin 0.0125% Placebo	Capsaicin > placebo Reduction in pain Reduction in stiffness Improvement in function
Chronic soft tissue pain			
Chrubasik et al,[20] 2010	Design: R, PC, DB, multicenter, N = 130 Duration: 3 wk	Capsaicin 0.05% 3 times a day Placebo	Capsaicin > placebo Reduction in pain

Civamide = cis-isomer of capsaicin; DB = double blind; PC = placebo controlled; R = randomized.

up to 4 patches are applied for 12 to 24 hours per day.[36] Dermal absorption of lidocaine varies based on the formulation, with lidocaine gel producing higher blood concentrations than the patch. The maximum concentration of lidocaine after application of the gel remains much lower than blood concentrations associated with antiarrhythmic therapy or toxicity.[48] The US Food and Drug Administration has cleared lidocaine for the management of postherpetic neuralgia, which typically presents as a burning pain, brief lancinating pain, hyperalgesia, and/or allodynia. A 2014 Cochrane review of the efficacy of topical lidocaine for the management of neuropathic pain found that lidocaine 5% plaster may be effective in treating neuropathic pain in a small number of patients and is well tolerated during short-term therapy. This review also included studies evaluating the 5% patch, 5% cream, 8% spray, and 5% gel, which had small sample sizes and incomplete outcome assessment as defined by reviewers.[49] Case reports also describe improvements in low back pain when lidocaine 5% patches are added to existing pain regimens.[50] Please see Table 3 for a summary of topical lidocaine clinical trial data.

Tricyclic Antidepressants

The peripheral mechanism of analgesia exerted by topical antidepressants has not been completely described. Tricyclic antidepressants (TCAs) are believed to block neuronal sodium channels in a fashion similar to the actions of lidocaine, but TCAs also inhibit noradrenaline

TABLE 2: Topical nonsteroidal anti-inflammatory clinical trials

Study, osteoarthritis	Study characteristics	Treatment arms	Results
Altman et al,[42] 2009	Design: R, DB, PC, parallel group N = 385 Duration: 8 wk	Diclofenac 1% 4 times daily Placebo	Diclofenac > placebo Reduced pain intensity
Baer et al,[43] 2005	Design: R, DB, PC, parallel group N = 216 Duration: 6 wk	Diclofenac 1.5% 4 times daily Placebo	Diclofenac > placebo Reduction in pain, reduction in stiffness, improvement in physical function
Baraf et al,[44] 2011	Design: R, DB, PC, parallel group N = 1426 Duration: 12 wk	Diclofenac 1% 4 times daily	Diclofenac > placebo Reduction in pain and in pain on movement, improvement in physical function
Dickson,[45] 1991	Design: R, DD, AC parallel groups N = 235 Duration: 4 wk	Piroxicam 0.5% 3 times daily + placebo tab Ibuprofen 400 mg + placebo cream 3 times daily	Piroxicam = oral ibuprofen

AC = active controlled; DB = double blind; DD = double dummy; PC = placebo controlled; R = randomized.

TABLE 3: Topical lidocaine clinical trials

Study, neuropathic pain	Study characteristics	Treatment arms	Results
Binder et al,[51] 2009	Design: enriched enrollment randomized to DB, PC	Lidocaine 5% plaster	Lidocaine > placebo
	Crossover	Placebo	Patients switched to placebo reported worsening pain intensity and pain relief
	N = 71		
	Duration: 8 wk		
	(Open label)		
	2 wk		
	(DB, R, withdrawal)		
Galer et al,[52] 1999	Design: enriched enrollment randomized to DB, PC	Lidocaine 5% plaster	Lidocaine > placebo
	Crossover	Placebo plaster	Longer median time to exit, higher percentage of patients with a lot or complete relief of pain 5 or more days of 14
	N = 32		
	Duration: 4 wk (open label)		
	2 wk		
	(DB, R, withdrawal)		
Meier et al,[53] 2003	Design: R, PC, DB, crossover	Lidocaine 5% plaster	Lidocaine > placebo
	N = 58	Placebo plaster	≥50% pain reduction
	Duration: 7 d		

DB = double blind; PC = placebo controlled; R = randomized.

and serotonin reuptake. They also interact with Ca^{++} and K^{+} channels and receptor systems (e.g., acetylcholine, histamine, opioid, α-adrenoceptors, β-adrenoceptors) involved in pain regulation.[54] Antidepressants are also believed to inhibit the release of inflammatory mediators.[46,55] TCAs that have been studied or suggested for pain management include amitriptyline, imipramine, and doxepin. Although not indicated for neuropathic pain, topical doxepin is commercially available as a 5% cream that the US Food and Drug Administration has cleared for the short-term management of moderate pruritus secondary to atopic dermatitis or lichen simplex chronicus.

Very few data have been published on the safety or efficacy of topically applied TCA products. At least one published report details severe toxicity in a pediatric patient after exposure to a topical compound containing imipramine and multiple other medications, which highlights the potential for systemic absorption and resulting harm.[56] Published reports have documented variable results after topical administration of amitriptyline for neuropathic pain syndromes, with more favorable results generally reported when higher concentration (5%-10%) preparations are used.[57-59] One case report on the use of amitriptyline for central neuropathic pain from multiple sclerosis suggests that effects were likely systemic, because the patient reported analgesia when topical amitriptyline was applied to an area distal to the site of pain, and sedation was reported following the administration of 10% cream.[60] Other studies involving compounded products containing amitriptyline have also demonstrated variable analgesic effects and the possibility of some systemic absorption.[61-63] This may indicate that topical amitriptyline application has a notable risk of precipitating CNS side effects, which would be dangerous for older adult patients. Doxepin has also been studied for topical use in patients with neuropathic pain but was noted to take approximately 2 weeks for onset of overall analgesia. In addition, 3.3% topical doxepin was reported to have no significant effect on component symptoms, such as numbness, pins and needles, sensitivity, and shooting pain.[64,65] When prescribing topical antidepressants, it would be important to continue to counsel patients on the possibility of CNS and anticholinergic effects and to monitor for signs of systemic adverse events, because studies appear to demonstrate continued risk even with topical administration. Please see Table 4 for a summary of topical TCA clinical trial and case report data.

Clonidine

Clonidine is an α_2 adrenergic receptor agonist that works in the periphery to reduce sensory nerve excitation by activating G protein-coupled α_2 adrenergic receptors on cutaneous nociceptors, and by releasing inhibitory G proteins, which downregulate adenylate cyclase and other secondary messengers involved in the initiation and maintenance of abnormal excitation.[68] Clonidine also reduces cytokine production and improves blood flow.[69] A study that evaluated the safety and efficacy of 0.1% topical clonidine gel for diabetic peripheral neuropathy suggests topical clonidine preparations may significantly

TABLE 4: Topical tricyclic antidepressant clinical trials

Study	Study characteristics	Treatment arms	Results
Neuropathic pain			
Ho et al,[59] 2008	Design: DB, R, PC N = 35 Duration: 1 wk	Amitriptyline 5% Lidocaine 5% Placebo	Amitriptyline = placebo Lidocaine > placebo
Lynch et al,[61] 2003	Design: DB, R, PC Crossover N = 20 Duration: 2 d	Amitriptyline 1% Ketamine 0.5% Combination Placebo	Amitriptyline = ketamine = combination = placebo
Lynch et al,[66] 2005	Design: DB, R, PC N = 92 Duration: 3 wk	Amitriptyline 2% Ketamine 1% Combination Placebo	Amitriptyline = ketamine = combination = placebo
McCleane,[64] 2001	Design: DB, R, PC N = 200 Duration: 4 wk	Doxepin 3.3% Capsaicin 0.025% Combination Placebo	Doxepin = capsaicin = combination All significantly reduce pain to a similar extent
Chemotherapy-induced peripheral neuropathy			
Gewandter et al,[63] 2014	Design: DB, R, PC, multicenter N = 462 Duration: 6 wk	Amitriptyline 4% + ketamine 2% Placebo	Amitriptyline + ketamine = placebo
Postherpetic neuralgia			
Lockhart,[67] 2004	Design: multicenter enriched enrollment study, randomized withdrawal N = 250 Duration: 1 wk 2 wk	Amitriptyline 4% + ketamine 2% Amitriptyline 2% + ketamine 1% Placebo	Amitriptyline 4% + ketamine 2% > placebo High percentage of patients with ≥30% pain reduction during last 2 wk
Diabetic peripheral neuropathy			
Kopsky et al,[60] 2012	Design: case report N = 1 Duration: 7 mo	Amitriptyline 5% (hands) Amitriptyline 10% (feet)	Total reduction of pain within 20 min
Neuropathic pain			
Kopsky et al,[60] 2012	Design: case report N = 1 Duration: 1 wk	Amitriptyline 10% (feet)	Complete resolution of pain, with slowing of thoughts and difficulty concentrating, which led to discontinuation
Complex regional pain syndrome			
McCleane,[65] 2002	Design: case report N = 1 Duration: 2 wk	Doxepin cream (concentration not reported)	Reduction in pain, and thermal and mechanical allodynia

DB = double blind; PC = placebo controlled; R = randomized.

reduce pain in patients who have functional and possibly sensitized nociceptors in the affected skin. Although patients treated with clonidine gel had significantly greater reductions in pain, there was not a statistically significant difference in the number of patients who experienced a ≥30% or ≥50% reduction in pain after 12 weeks of therapy.[68] Topical clonidine has also been studied for the management of orofacial pain.[70] Clonidine transdermal patches, which have long been used for the management of hypertension, have been reported to

TABLE 5: Topical clonidine clinical trials

Study	Study characteristics	Treatment arms	Results
Diabetic peripheral neuropathy			
Byas-Smith et al,[74] 1995	Design: enriched enrollment	Transdermal clonidine (titrated from 0.1 to 0.3 mg/d)	Phase 1: clonidine = placebo
	N = 41	Placebo	Comparable reduction in mean pain intensity scores
	Duration: 3-wk intervals (phase 1)		Phase 2 (clonidine responders): clonidine > placebo
	1-wk intervals (phase 2)		Reduced pain intensity
Campbell et al,[68] 2012	Design: DB, R, PC	Clonidine 0.1% gel	Clonidine caused a nonsignificant reduction in foot pain
	N = 182	Placebo	
	Duration: 12 wk		
Orofacial pain			
Epstein et al,[70] 1997	Design: open label	Clonidine 0.2 mg/g	Patients with oral neuralgialike pain responded more favorably to clonidine cream than patients with oral neuropathic pain
	N = 17		
	Duration: 4 wk (initial followup, optional continuation)		

DB = double blind; PC = placebo controlled; R = randomized.

TABLE 6: Topical ketamine clinical trials

Study	Study characteristics	Treatment arms	Results
Complex regional pain syndrome			
Finch et al,[77] 2009	Design: DB, PC, crossover	Ketamine 10%	Ketamine applied to the symptomatic limb inhibited allodynia to light brushing and hyperalgesia to punctate stimulation
	N = 20	Placebo	
	Duration: n/a		
Peripheral neuropathy			
Lynch et al,[61] 2003	Design: DB , R, PC, crossover	Amitriptyline 1%	Amitriptyline = ketamine = combination = placebo
	N = 20	Ketamine 0.5%	
	Duration: 2 d	Combination	
		Placebo	
Lynch et al,[79] 2005	Design: DB, R, PC	Amitriptyline 2%	Amitriptyline = ketamine = combination = placebo
	N = 92	Ketamine 1%	
	Duration: 3 wk	Combination	
		Placebo	
Postherpetic neuralgia			
Barros et al,[80] 2012	Design: DB, R, PC, crossover study	Ketamine 1%	Ketamine = placebo
	N = 12	Placebo	
	Duration: 15 d		
Diabetic peripheral neuropathy			
Mahoney et al,[81] 2012	Design: DB, R, PC	Ketamine 5%	Ketamine = placebo
	N = 17	Placebo	
	Duration: 4 wk		

DB = double blind; PC = placebo controlled; R = randomized; n/a = not applicable.

TABLE 7: Topical baclofen clinical trials

Study	Study characteristics	Treatment arms	Results
Chemotherapy-induced peripheral neuropathy			
Barton et al,[86] 2011	Design: DB, R, PC	Baclofen 10 mg + amitriptyline 40 mg + ketamine 20 mg in pluronic lecithin organogel	Baclofen + amitriptyline + ketamine > placebo
	N = 208 Duration: 4 wk	Placebo	Significant improvement in motor neuropathy, trend toward improved sensory neuropathy
Neuropathic pain			
Kopsky et al,[85] 2013	Design: case report N = 1 Duration: 6 mo	Baclofen 5% reduced to baclofen 2%	95% reduction in pain compared with baseline
Vulvodynia and proctodynia			
Keppel Hesselink et al,[83] 2014	Design: case report N = 1 Duration: 3 mo	Baclofen 5 % + palmitoylethanolamide 400 mg	≥50% reduction in symptoms

DB = double blind; PC = placebo controlled; R = randomized.

provide some pain relief in certain patients with diabetic peripheral neuropathy. Clonidine, however, would also be expected to produce significant systemic effects, such as hypotension.[71] The Beers list even recommends avoiding clonidine as first-line therapy for hypertension in elderly patients because of the high risk of CNS adverse effects, orthostatic hypotension, and bradycardia.[5] Pharmacokinetics studies indicate there is a linear relationship between clonidine transdermal patch size (the surface area of administration, not reservoir size) and serum drug concentrations. The pharmacokinetics of topical/compounded clonidine preparations are unknown and would be expected to vary based on vehicle selection, but are likely also related to the surface area of administration.[72] This theory is strengthened by the fact that less pain reduction was reported among study participants who received 0.2% topical clonidine over a smaller surface area than those who received 0.1% topical clonidine over a larger surface area.[73] Given the risk of hypotension, rebound hypertension, and sedation, it would not be advisable to initiate transdermal clonidine for elderly patients with no cardiovascular indication. Caution should be used with compounded products containing clonidine, especially when applied over a large surface area. Please see Table 5 for a summary of topical clonidine clinical trial data.

Ketamine

Ketamine is an NMDA receptor antagonist. Glutamate is released from primary afferent nerve endings and keratinocytes as a result of inflammation or tissue damage in high concentrations, leading to activation of NMDA and other glutamate receptors responsible for sensory nerve activation. NMDA increases the excitability of peripheral and central nociceptors and is thought to be involved in the development of hyperalgesia and allodynia.[36] Recent animal studies have suggested the nitric oxide/cyclic guanosine monophosphate pathways and adenosine triphosphate-sensitive K^+ channels have a role in the peripheral analgesic effects of ketamine.[75,76] In a small, double-blind, placebo-controlled crossover trial, ketamine 10% cream inhibited allodynia to light brushing and punctate hyperalgesia when applied to the symptomatic limb of patients with complex regional pain syndrome. In that study there was no detectable systemic absorption. The dose of cream was limited to 0.5 mL, which was generally enough to cover the testing area, and efficacy was evaluated after single applications separated by at least 1 week, not multidose exposure.[77] Several case reports have also been published describing positive analgesic effects of various concentrations of topical

Drug Name	Quantity	Drug Cost
Baclofen 100%	14.4	$561.95
Cyclobenzaprine HCl 100%	7.2	$365.44
Versapro cream base	190.8	$669.18
Propylene glycol 99.5%	36	$7.79
Gabapentin 100%	21.6	$1,416.25
flurbiprofen	72	$2,885.81
Lidocaine HCl 100%	18	$84.47
Ingredient cost submitted		$5,990.89
Cost approved		$5,839.99

FIGURE: Sample compounded pain medication cost submission

TABLE 8: Summary of selected topical pain medications

Medication	Medication characteristics
High-concentration capsaicin	Target: neuropathic pain
	Preparations: qutenza 8% patch
	Considerations: similar efficacy to oral agents for neuropathic pain
	High cost of administration
	Patients often experience significant postapplication pain which may lead to an increase in blood pressure
	Adverse effects include mild to moderate erythema, pain, papules, pruritus, and swelling
Low-concentration capsaicin (brand, generic, OTC)	Target: chronic soft tissue pain; osteoarthritis; low back pain
	Preparations: cream (0.025%, 0.035%, 0.075%, 0.1%)
	Gel (0.025%)
	Lotion (0.025%)
	Patch (0.025%, 0.0375%, 0.05%)
	Considerations: moderate efficacy reported
	Transient burning following administration
	Adverse effects include local burning, itching, or stinging sensation
Diclofenac (brand, generic)	Target: inflammatory pain
	Preparations: cream (1%, 3%)
	Gel (1%, 3%)
	Patch (1.3%)
	Solution (1.5%, 2%)
	Considerations: may cause increased risk of cardiovascular events, MI, stroke
	May cause increased risk of serious gastrointestinal adverse reactions, but this risk is lower than the risk associated with oral diclofenac
	May cause significant elevations in hepatic transaminases
Flurbiprofen, Ibuprofen, Ketoprofen, Piroxicam	Target: inflammatory pain
	Preparations: compound only (variable concentrations recommended)
	Considerations: dermatologic reactions are the most common form of adverse event
	The risk of gastrointestinal reactions is significantly lower than it is for oral NSAIDs
Lidocaine (brand, generic, OTC)	Target: neuropathic pain; low back pain
	Preparations: cream (3%, 4%, 5%)
	Gel (2%, 3%, 4%, 5%)
	Lotion (3%)
	Ointment (5%)
	Patch (5%)
	Considerations: expect very minimal systemic absorption of lidocaine with up to 4 patches applied for 12-24 h
	Some patients report increased pain when the patch is left on for more than 18 h
Doxepin (brand)	Target: neuropathic pain
	Preparations: cream (5%)
	Considerations: there is not strong evidence to support the efficacy of topical antidepressants without high concentrations
	Application of topical TCAs may lead to systemic absorption significant enough to cause anticholinergic effects, such as confusion, sedation, delirium, urinary retention, and constipation, which should be avoided in older adult patients

TABLE 8: Summary of selected topical pain medications (continued)

Medication	Medication characteristics
Amitriptyline, Imipramine	Target: neuropathic pain
	Preparations: compound only (variable concentrations recommended)
	Considerations: there is not strong evidence to support the efficacy of topical antidepressants without high concentrations
	Application of topical TCAs may lead to systemic absorption significant enough to cause anticholinergic effects, such as confusion, sedation, delirium, urinary retention, and constipation, which should be avoided in older adult patients
Clonidine	Target: neuropathic pain
	Preparations: compound only (variable concentrations recommended)
	Considerations: transdermal clonidine patches should not be initiated for pain control in older adult patients
	Use caution when including clonidine in compounded products because of the increased risk of CNS adverse effects, orthostasis, and bradycardia
Ketamine	Target: neuropathic pain
	Preparations: compound only (variable concentrations recommended)
	Considerations: there is variable evidence to support the efficacy of topical ketamine for neuropathic pain
	No systemic absorption is expected with concentrations up to 10%
Baclofen	Target: inflammatory pain; neuropathic pain (in combination)
	Preparations: compound only (variable concentrations recommended)
	Considerations: very little information is available about the efficacy and systemic absorption of topical baclofen. Patients should be monitored for signs of CNS side effects if prescribed compounds containing baclofen
	Patients should not be prescribed topical baclofen in combination with oral baclofen, a therapeutic duplication that may increase the risk of systemic side effects

CNS = central nervous system; MI = myocardial infarction; NSAID = nonsteroidal anti-inflammatory drug; OTC = over-the-counter; TCA = tricyclic antidepressant.

ketamine for neuropathic pain syndromes. However, 4 placebo-controlled trials (ketamine 0.5% to ketamine 5%) found no significant difference in analgesia between treatment and control groups.[78] Please see Table 6 for a summary of topical ketamine clinical trials.

Baclofen

Baclofen is a gamma-aminobutyric acid B ($GABA_B$) agonist. In the periphery, activation of $GABA_B$ receptors located on cutaneous fine nerve endings and keratinocytes causes a decrease in Ca^{++} membrane conductance and an increase in K^+ membrane conductance, to inhibit transmission. Research suggests the peripheral analgesic activity of baclofen is the result of activation of tetraethylammonium-sensitive K^+ channels.[82] Baclofen may also have some antiglutamate activity, which could potentially interact with ionotropic glutamate receptors expressed in the unmyelinated nociceptive fibers in mammalian skin.[83] Peripherally applied ionotropic glutamate receptor antagonists attenuate nociceptive scores in a model for inflammatory pain.[84] One published case report described the resolution of neuropathic pain in the legs of a patient with acromegaly as well as a report of topical baclofen 5% given in combination with oral palmitoylethanolamide to effectively manage chronic vulvodynia and proctodynia.[83,85] A topical gel containing baclofen, amitriptyline, and ketamine studied in a placebo-controlled trial for the management of chemotherapy-induced peripheral neuropathy showed a trend in favor of the compound, but it did not provide a statistically significant reduction in pain compared with placebo.[86] Please see Table 7 for a summary of topical baclofen clinical trial and case report data.

Cost

During the past 4 years, pharmacy benefit management companies and managed care organizations have noticed a steady increase in the cost of bulk compounding ingredients, which led to significant increases in compounded drug costs. CenterLight Healthcare, a New York managed care organization, experienced a 677.3% increase in plan cost per member per month for compounded medications from January 2014 to August 2014 compared with January 2013 to August 2013. This increase reflects an increase in the number of compounded prescriptions and the increasing average wholesale price

for bulk powders, creams, and gel bases. In many cases compounded products are billed to insurance based on cumulative ingredient cost (Figure), which is calculated based on average wholesale price. As ingredient costs have risen, the cost of monthly compounded products has also risen up to thousands of dollars. As a result of increasing costs, many prescription drug plans are choosing to stop covering compounded drug products or to implement customized ingredient lists that exclude many bulk powders and other topical ingredients. Physicians may receive advertisements from compounding pharmacies that include suggested ingredient combinations for pain management and anecdotal reports of efficacy. Unfortunately, the estimated cost of compounds is not often disclosed to prescribers, and older adult patients may not be able to afford them if they are not covered by insurance. As such, it would be ideal to limit the ingredients in compounded products to only those with perceived benefit and to avoid including multiple ingredients of the same therapeutic class. Prescribers may also consider inquiring about estimated prescription costs before ordering these medications for their patients.

Conclusion

Given the high risk associated with chronic prescribing of many oral pain medications used to treat neuropathic, inflammatory, and musculoskeletal pain, it is reasonable for prescribers to consider incorporating topical pain medications into the regimens of their older adult patients. Commercially available or compounded topical pain medications may be used to replace or augment doses of oral medications in an effort to decrease the risk of adverse drug events. When selecting topical pain medications prescribers should consider the type of pain being targeted, the potential analgesic effects of the medications selected (eg, anti-inflammatory, neuropathic), and the potential for systemic absorption and related side effects (Table 8). Prescribers should also be conscious of the rising costs of many compounded pain medications and possible limitations in availability. It is also important to remember there is a large amount of interpersonal and intrapersonal variability in medication absorption and analgesic effect, so patients should be routinely reassessed to ensure that topical medications are providing a noticeable improvement in symptoms without adverse reactions.

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