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REVIEW ARTICLE

Topical Treatment of Localized Neuropathic Pain in the Elderly

Gisèle Pickering[1,2] · **Camille Lucchini**[1]

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Abstract
The prevalence of neuropathic pain in the older population has been reported to be very high and is most commonly localized to a circumscribed area. Treatment failure is frequent in neuropathic pain and is accompanied by central side effects with recommended oral drugs acting on the central nervous system. A number of topical pharmaceuticals are available on prescription and also sold over the counter. This review in persons aged older than 60 years shows the efficacy of lidocaine 5% and capsaicin 8% for localized neuropathic pain while results with other pharmaceuticals are rather inconsistent. Local application of drugs has a very limited systemic effect and the pharmacological advantages of local over systemic treatment are particularly interesting in older persons who often have comorbidities and take multiple medications. However, more information is needed on the efficacy and safety of lidocaine 5% and capsaicin 8% in older old persons and on the long-term effects of these pharmaceuticals. These studies should also pave the way for research and development in the field of topical analgesics with a satisfactory level of evidence-based medicine.

Key Points

Topical analgesics, especially lidocaine 5% and capsaicin 8%, are recommended for neuropathic pain management but there is a paucity of publications in older persons.

More information is needed on their efficacy and safety in older old persons and on prospective long-term use.

1 Introduction

The prevalence of chronic pain is high in older people, estimated to be 25–85% [1]. Neuropathic pain (NP), a type of chronic pain, is defined by the International Association for the Study of Pain as "pain that arises as a direct consequence of a lesion or disease affecting the somatosensory system" [2], may be central or peripheral, and is often accompanied by incomplete relief of recommended drugs (antidepressants anti-epileptic drugs, opioids). The prevalence of NP in the older population has been reported to be dramatically high, up to 32% [1] and 40% [3] and is probably underestimated [4]. The quality of life of patients with NP is often impaired and NP can aggravate functional decline in aging [5]. Localized NP (LNP) is the most common presentation of NP, affecting about 60% of patients with NP, and is defined as 'a type of peripheral neuropathic pain that is characterized by consistent and circumscribed area(s) of maximum pain associated with abnormal sensitivity of the skin and/or spontaneous symptoms characteristic of neuropathic pain, for example, burning pain' [6]. This core definition of LNP was elaborated on by the expert panel to help clinicians better characterize LNP and determine the choice of first-line treatment [7], and it was followed by a consensus on topical approaches to alleviate LNP [8]. The expert panel considered 5% lidocaine and 8% capsaicin plasters as first-line drugs for LNP treatment in adult persons, especially in patients with comorbidities and polypharmacy. The rationale of both drugs is that pain transmission to the central nervous system by afferent nociceptive fibers can be interrupted by the local application of blocking drugs with no (or extremely limited) systemic effect. Topical pharmaceuticals

✉ Gisèle Pickering
gisele.pickering@uca.fr

[1] Clinical Pharmacology Department, CPC/CIC Inserm 1405, Clermont-Ferrand University Hospital, Clermont-Ferrand, France

[2] Centre de Pharmacologie Clinique, CPC/CIC Inserm 1405, Bâtiment 3C, CHU Clermont-Ferrand, 58 rue Montalembert, BP 69, 63003 Clermont-Ferrand Cedex 1, France

are available by prescription and over the counter and lidocaine 5% and capsaicin 8% patches are recommended [6, 9].

This review aims to evaluate the efficacy and safety of topical pharmaceutical agents available to treat LNP in older persons. Topical treatment for LNP may be an important option for aging persons taking multiple medications and has the advantage of targeting the area of pain and limiting adverse events (AEs) and drug interactions.

A literature review was conducted through an exhaustive electronic search of MEDLINE, PubMed, Google Scholar, and Cochrane databases. Keywords such as "lidocaine plaster", "topical treatments", "topical analgesic", "transdermal patches", "capsaicin patch", "elderly", "older", and "localized neuropathic pain" were used without limitation in language or date of publication. The last search was conducted in September 2019. It was restricted to reviews, Cochrane reviews, and randomized controlled trials (RCTs), comparing a topical agent (lidocaine, capsaicin, ketamine, amitriptyline) with placebo or an active control for capsaicin and elderly was defined as over the age of 60 years. Over-the-counter preparations for LNP were also searched with keywords such as "plants", "herbal", "plaster", "cream", and "gel".

2 Topical Treatments

Among 195 eligible publications, after having discarded duplicates and screened abstracts, 18 RCTs were included in this review (Table 1), all involved lidocaine or capsaicin topical treatment. All studies included a number of elderly persons. Five reviews [6, 10–13], including three Cochrane reviews in adults [10–12], other articles in elderly patients [14] and comorbid patients [15, 16], and other reviews for topical analgesics in older persons have been published [17, 18]. Since the 2014 review [13], three additional RCTs have been published, one study on lidocaine [19] and two studies on capsaicin [20, 21].

2.1 Topical Lidocaine

A total of ten RCTs [19, 22–30] included 756 patients (aged > 60 years), with post-herpetic neuralgia (PHN) [22–25, 27, 29, 30], PHN or diabetic neuropathic pain [26], cancer-related LNP [28], or post-surgery LNP [19]. One Cochrane review was published [10]. Lidocaine patch 5% (700 mg with a maximum of three patches a day) [19, 23–28, 30], lidocaine 5% in gel [22], and lidocaine 8% in spray [29] were reported.

Efficacy was the primary outcome in most studies [19, 22–29], using different indicators: changes in pain scores, response rate, time to exit, dynamic mechanical allodynia. Changes in cognitive function was the primary outcome in Pickering et al. [30].

Changes in pain scores [22, 23, 25, 28, 29] were evaluated for 12 h ($n = 35$, mean age: 75 years with a range of 50–90 years) [23], for 24 h ($n = 39$, mean age: 70 years with a range of 55–85 years) [22], at 15 min post-spray ($n = 24$, mean age: 71 years with a range of 32–91 years) [29], or after 3 weeks ($n = 96$, mean age: 74 ± 8.3 years) [25]. All studies showed improvements in favor of lidocaine topical treatment, except one study [28] for 4 weeks ($n = 28$, mean age: 61.8 ± 0.5 years).

Response rate (reduction averaged over the last 3 days from baseline of ≥ 2 points) was evaluated for 4 weeks ($n = 311$, mean age: 62.6 ± 10 years) in one study [26] and suggested that the 5% lidocaine-medicated plaster was more effective than pregabalin in patients with PHN. Time to exit (a decrease of 2 points for 2 consecutive days in the pain relief score) was evaluated with a 6-point verbal pain rating scale for 14 days [24, 27]. In Galer et al. ($n = 32$, mean age: 77.4 years with a range of 62–96 years, 69% were aged > 75 years), time to exit was more than 14 days compared with 3.8 days for the vehicle patch ($p < 0.001$) [24]. In Binder et al. ($n = 36$, mean age: 72.5 ± 8.5 years), time to exit was 13.5 days for patients treated with lidocaine compared with 9 days for patients treated with placebo ($p = 0.1510$) [27]. In one study [19], the response to treatment was evaluated with dynamic mechanical allodynia (a decrease of $\geq 30\%$ dynamic mechanical allodynia) for 3 months ($n = 36$, mean age: 69.5 ± 7.3 years with a range of 18–80 years). After 3 months treatment, the percentage of responders was overall higher for lidocaine 5% than placebo (95.8% vs 58.3%; $p = 0.003$). The impact of treatment on cognition in patients with PHN ($n = 40$, mean age: 72 ± 8 years) was studied using Cantab® tests [30] and revealed that systemic treatment (antidepressants, anti-epileptic drugs) impaired cognition while the lidocaine 5% patch did not have deleterious effects on cognitive parameters.

All but one study [28] showed a great improvement in pain and concluded that topical lidocaine is an effective treatment for LNP. Secondary outcomes included improvements of quality of life, cognition, and patient satisfaction using the Brief Pain Inventory, Short Form Health Survey, Euroquol in 5 Dimensions, Patient Global Impression of Change, Clinical Global Impression of Change, Short-Form McGill Pain Questionnaire, and self-assessment treatment.

In Cheville et al., all Brief Pain Inventory interference scores improved to a greater degree in the lidocaine group in both physical (general activity, $p = 0.02$; work, $p = 0.04$) and psycho-emotional (mood, $p = 0.06$; relationships with others, $p = 0.02$) domains [28]. Baron et al. showed a greater quality of life with Euroquol in 5 Dimensions in the lidocaine

Table 1 Randomized clinical trials with topical analgesics

First author, year	Age, years	No. of patients	Pathology	Treatment	Primary outcome	Primary outcome measures	Secondary outcomes
Lidocaine							
Rowbotham, 1995	75 [55–85]	50	PHN	Gel 5%	Pain changes	Pain intensity (VAS)	Blood lidocaine concentrations
Rowbotham, 1996	70 [50–90]	39	PHN	Patch 5%	Pain changes	Pain intensity (VAS)	Blood lidocaine concentrations Symptom checklist
Galer, 1999	77.4 [62–96]	32	PHN	Patch 5%	Pain changes	Time to exit	CGIC
Galer, 2002	74 ± 8.3	96	PHN	Patch 5%	Pain changes	NPS composite score	NPS descriptors
Baron, 2009	62.6 ± 10	311	PHN or DNP	Patch 5%	Pain changes	Response rate	Eq5D PGIC
Binder, 2009	72.5 ± 8.5	36	PHN	Patch 5%	Pain changes	Time to exit	Daily pain intensity Daily pain relief Daily pain reduction NRS
Cheville, 2009	61.8 ± 0.5	28	Cancer-related LNP	Patch 5%	Pain changes	Pain intensity (NPRS)	BPI
Kanai, 2009	71 (32–91]	24	PHN	Spray 8%	Pain changes	Pain intensity (VAS)	
Pickering, 2014	69.5 ± 7.3	40	PHN	Patch 5%	Cognitive function changes	Cantab® tests	
Pickering, 2019	72 ± 8	36	Post-surgery LNP	Patch 5%	Pain changes	DMA	Size of painful area
Capsaicin							
Bernstein, 1989	72.3 [54–90]	32	PHN	0.075% cream	Pain changes	Pain intensity (NPRS)	
Backonja, 2008	71.5 ± 11.6	402	PHN	Patch 8%	Pain changes	NPRS Weeks 2–8	% of responders
Backonja, 2010	74.4 ± 7.4	44	PHN	Patch 8%	Pain changes	NPRS Days 8–28	PGIC/CGIC
Webster, 2010a	68.7 ± 12	155	PHN	Patch 8%	Pain changes	NPRS Weeks 2–8	% of responders
Webster, 2010b	71.6 ± 10.27	199	PHN	Patch 8%	Pain changes	NPRS Weeks 2–8	% of responders
Irving, 2011	70.2 ± 12.25	418	PHN	Patch 8%	Pain changes	NPRS Weeks 2–8	% of responders
Moon, 2017	69.6 ± 8.2	60	PHN or DNP	0.625% or 1.25%	Pain changes	NPRS Weeks 2–5	% of responders
Simpson, 2017	63.9 ± 10.6	369	DNP	Patch 8%	Pain changes	NPRS Weeks 2–8	% of responders

BPI Brief Pain Inventory, *CGIC* Clinical Global Impression of Change, *DMA* dynamic mechanical allodynia, *DNP* diabetic neuropathic pain, *Eq5D* Euroqol 5 Dimensions, *LNP* localized neuropathic pain, *NPRS* Numeric Pain Rating Scale, *NPS* Neuropathic Pain Scale, *NRS* Numeric Rating Scale, *PGIC* Patient Global Impression of Change, *PHN* post-herpetic neuralgia, *VAS* Visual Analog Scale, % of responders (≥30% pain intensity decrease)

group, and a greater patient satisfaction evaluated with the Patient Global Impression of Change [26]. Concerning the severity of allodynia, Baron et al. showed a larger decrease in patients with PHN treated with the lidocaine patch [26]. Galer et al. also showed a better satisfaction with lidocaine treatment ($p < 0.001$) [24]. Binder et al. had an improvement in all secondary outcomes studied such as daily pain intensity ($p = 0.0289$) and daily pain reduction ($p = 0.0040$), except the mean pain relief in the last week [27]. The most recent study, Pickering et al., showed a significant decrease in the size of the painful area, an improvement in the cold

pain threshold ($p = 0.001$), and a decrease in pain intensity ($p = 0.045$) [19].

Finally, concerning safety, all studies reported AEs linked to the local application site (erythema, burning, rash, redness) for the majority of patients. All AEs were considered of 'mild' or 'moderate' severity and some patients discontinued the studies.

2.2 Topical Capsaicin

A total of eight RCTs with 1779 patients [20, 21, 31–36] with PHN [31–36], diabetic neuropathic pain [21], or both [20] were retrieved. Cochrane reviews studied low- and high-dose capsaicin treatment [10, 12]. Studies compared the capsaicin 8% patch [21, 32–36] or 0.075% cream [31] to the control, 0.04% capsaicin, to maintain double blinding and possible side effects. A comparison was also published of 0.625% and 1.25% capsaicin patches to a 0.04% patch [20]. Other publications that mentioned the age of the patients were also included, otherwise they were not reviewed.

Efficacy was the primary outcome, evaluated with the percentage reduction in average pain between weeks 2 and 8 ($n = 402$, mean age: 71.5 ± 11.6 years [32]; $n = 369$, mean age: 63.9 ± 10.6 years [21]; $n = 155$, mean age: 68.7 ± 12.0 years [34]; $n = 299$, mean age: 71.6 ± 10.27 years [35]; $n = 418$, mean age: 70.2 ± 12.25 years with a range of 18–90 years) [36], weeks 2 and 5 ($n = 60$, mean age: 69.6 ± 8.2 years, with a range of 46–86 years) [20], days 8–28 ($n = 44$, mean age: 74.4 ± 7.4 years with a range of 18–90 years) [33], and with pain intensity and relief ($n = 32$, mean age: 72.3 years with a range of 54–90 years) [31]. All studies but one [34] showed a statistically significant pain reduction with capsaicin, patient satisfaction, and an improved quality of life.

Secondary outcomes included the percentage of responders [20, 21, 32, 34–36] and patient satisfaction. Only three studies found significant results: Backonja et al. (baseline to weeks 2–12, $p = 0.05$) [32], Simpson et al. (baseline to weeks 2–12, $p = 0.05$) [21], and Irving et al. (baseline to weeks 2–8, $p = 0.04$) [36]. Patient Global Impression of Change and Clinical Global Impression of Change were evaluated in all articles but Backonja et al. [33], and more patients regarded themselves as improved in the capsaicin group than in the control group. For all other variables studied, in all studies, no significant difference was found between groups.

Safety was evaluated and patients in both groups had AEs with a maximum of 99% [32]. Severe AEs were reported [21, 32–34, 36], including increased blood pressure, atrial fibrillation, severe burning sensation, severe application-site pain, diarrhea, arthritis, or pneumothorax. Pain during application was relieved with oxycodone. Some articles also performed blood pressure tests [21, 32], reporting an increase in blood pressure related to greater pain, but returning to a normal level at withdrawal of the patch. No blood laboratory test changes have been observed [33–36]. Capsaicin 8% appears to be an effective treatment for the elderly but causes AEs and not all treated patients respond. A network analysis that included older persons (mean age ranged from 48 to 76 years) recently suggested that the efficacy observed with the capsaicin 8% patch is similar to that observed with oral agents (i.e., pregabalin, duloxetine, gabapentin) in patients with diabetic neuropathy. The oral agents were associated with a significantly elevated risk of somnolence, dizziness, fatigue, and discontinuation because of AEs compared with placebo [7, 8, 15].

2.3 Other Topical Pharmaceuticals

No specific RCTs with other treatments have been published. Other topical treatments for NP have been studied in the literature including local anesthetics (bupivacaine and mepivacaine), phenytoin, muscle relaxants (baclofen), α2-adrenergic agents (clonidine), and even a combination of these treatments but not in elderly patients. Several reviews have been published [3, 37–39]. Several other studies included a few older patients but do not allow conclusions to be drawn on their safety or efficacy in the global elderly population. Results of topical amitriptyline cream (1–5%) are inconsistent [40] or show no benefit, as a gel or cream, vs placebo [41–43], or AEs with 5–10% amitryptiline [40]. Amitriptyline 4% is also used in combination with ketamine 2% [43] but local redness was reported. Topical ketamine 0.5% or 1% (with and without amitriptyline) was not more effective on pain intensity than placebo [42–45]. Some case studies may be interesting, but very anecdotal, such as the case study of a 63-year-old patient with intractable NP relieved by loperamide 5% cream, a non-prescription opioid agonist used in diarrhea, for 2.5 h and able to reduce his daily intake of oxycodone [46]. Botanical oils are also used for pain relief with no proven benefit.

3 Discussion

Topical treatment of LNP is largely reported in evidence-based medicine, prescriptions, and in a variety of publications concerning over-the-counter treatments. One of the main observations is the pharmacological advantages of topical over systemic treatment, especially in elderly persons. International recommendations have been published for NP management [4, 9, 47] and pharmacological treatment with antidepressants, antiepileptic drugs, and opioids has a very limited efficacy with significant side effects that often limit long-term use. Concomitant medication and comorbidity often lead to poor patient compliance and unsatisfactory relief. Systemic drugs as well as pain itself

have central effects and may alter the cognitive architecture with negative impacts on various domains of cognition [30] including fatigue and sleep. The cognitive deficits widely observed in patients with NP taking antidepressants are not found with a 5% lidocaine-medicated plaster [30], an interesting alternative to alleviate pain and maintain cognitive integrity. Topical application offers a local delivery, a lower total systemic dose, and avoids first-pass metabolism [6]. Concomitant medication, especially in elderly persons, increases the potential risk of AEs and drug–drug interactions. These are induced by pharmacokinetic and pharmacodynamic age-related changes (decreased absorption, impaired distribution due to modified composition of body compartments, diminished hepatic metabolism and renal clearance, medication-related adverse effects) and major gastrointestinal adverse events, confusion, delirium, sedation, and memory loss in frail geriatric populations. Another advantage of topical administration is the possibility of combining other pharmacologic agents acting systemically, thus achieving an additive or synergistic effect without systemic drug interactions or additional side effects. The majority of local treatments are easy to administer and provide good patient adherence [48].

A large variety of formulations, including patches, creams, and gels, have been studied but they are not commercialized worldwide, not standardized, prescription only in some countries or over the counter in others, vary in price and indications, may be variable when extemporaneous [48, 49], and are subject to different health authority systems before release onto the market with formulation details missing or not fully described. Good quality data are often missing and beyond differences in formulations, poor efficacy may be linked to the etiology of NP and the area, location, and frequency of application [48]. Studies tend to have a short duration, small numbers of participants, not double blinded, and with a poor description of the placebo when there is one. The type of pain is often limited to PHN or post-diabetic neuropathy, while the main cause of NP is post-surgery NP [50]. Overall, there is little evidence for the efficacy of topical therapies except for topical lidocaine 5% and capsaicin 8% in adults [8], and even less evidence in the elderly because of a restricted number of publications.

Lidocaine is a local anesthetic available in plaster, spray, cream, or pharmaceutical preparations that acts with a non-selective blockade of both open and inactive voltage-dependent sodium channels in dermal nociceptors of C and A-δ primary afferent fibers. It may also activate some Transient Receptor Potential receptors in nociceptive sensory neurons [51]. Topical lidocaine 5% is a first- or second-line treatment in International Pain Society Guidelines [4, 8, 9, 51, 52]. Clinical experience and individual studies clearly indicate that it is effective for pain relief in older persons, although the Cochrane review in adults found no evidence from good quality RCTs to support the use of topical lidocaine to treat NP. We recently [19] reported in a double-blind placebo-controlled study with older persons that the lidocaine 5% patch has a significant impact on post-operative LNP characteristics, allodynia, and hyperalgesia compared with placebo. We stressed the therapeutic advantage of lidocaine for pain alleviation in older patients with several comorbidities and polypharmacy. The 5% lidocaine patch is easy to use, is sold over the counter in some countries, and may be applied by the patient him/herself, facilitating adherence to treatment [48]. Side effects are minor. A 'field-practice' study with a lidocaine 5% plaster was associated with a reduced need for other oral analgesics in elderly patients [14], and a recent retrospective study showed that patients receiving topical lidocaine benefited from long-term treatment.

Capsaicin is the active ingredient of chili peppers, available as a plaster or cream. It activates the Transient Receptor Potential Vanilloid 1 receptor and following continued capsaicin exposure, Transient Receptor Potential Vanilloid 1-containing sensory axons dysfunction, preventing pain transmission and resulting in a reduced pain response [8, 53]. Cochrane reviews [10, 12] on topical capsaicin found that high-concentration capsaicin (8%) is more effective than a lower concentration, but there is a low quality of evidence. For responder patients, there were additional improvements in sleep, fatigue, and quality of life. The patch is applied by a physician, not by the patient, for 30–60 min and may provide relief for up to 12 weeks but may be painful on application and is not available in all countries. Topical capsaicin is also available over the counter in some countries in concentrations of 0.025–0.075%, and although a systematic review found that it reduced pain [54], a Cochrane review found that there are insufficient data to draw conclusions [10]. Local adverse skin reactions early in treatment have been reported, but these disappeared after 1–2 weeks of treatment. However, there is no specific information on skin tolerance in elderly persons whose skin is thinner, and on the long-term effects and safety. Subgroup analyses would be helpful and should be conducted in future studies on a larger age range to pinpoint age specificities. A network analysis with capsaicin 8% concluded [15], in adults with a few older persons, that the efficacy of capsaicin was similar to systemic treatment, with less central effects, a point also made by Pickering et al. [30] with lidocaine 5% treatment. Other topical pharmaceuticals cannot be currently recommended in the light of poor and inconsistent results but could open interesting therapeutic and research options.

4 Conclusions

Studies in older persons show the efficacy of lidocaine 5% and capsaicin 8% for LNP. The pharmacological advantages of local over systemic treatment are particularly true for vulnerable patients and older patients with comorbidities and polypharmacy, who have an increased and latent risk of drug interactions. However, more information is needed on the efficacy and safety of lidocaine 5% and capsaicin 8% in older old persons and on the prospective long-term effects of these pharmaceuticals. These studies should also pave the way for research and development in the field of topical analgesics with a satisfactory level of evidence-based medicine in older persons who are particularly prone to develop LNP.

Compliance with Ethical Standards

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