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Counterirritants and Sensory Profiling of Pain-Relieving Patches

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ABSTRACT

Introduction: Musculoskeletal pain is a common medical and socioeconomic problem worldwide. Treatment and management options most commonly include analgesics such as paracetamol, nonsteroidal anti-inflammatory drugs (NSAIDs), and topical over-the-counter (OTC) preparations. Patients often use OTC topical analgesics owing to the benefits shown by clinical studies for the treatment and management of musculoskeletal injuries and disorders. The aim of this study was (1) to review the background, current understanding, and therapeutic usefulness of topical counterirritants for the management of musculoskeletal pain (2) and to evaluate the sensorial characteristics of two prototype patches containing counterirritants, designed to manage pain relief by delivering a warming or cooling sensation.

Methods: Detailed literature search was conducted in PubMed, Google Scholar, and Cochrane Library databases for this review. An expert sensory panel study comprising of ten trained sensory experts was conducted to evaluate the performance of prototype patches containing counterirritants for their sensory characteristics including overall sensation, cooling, warming, and tingling sensations, as well as functional parameters such as ease of application and removal, adhesive property, odor intensity, staining on clothes, residue or greasiness, and sweat/moistness on the skin after removal.

Results: Topical analgesics containing counterirritants like capsaicin, menthol, and salicylates produce analgesia by activating and then desensitizing epidermal nociceptors. Literature searches provide evidence for their use in the management of musculoskeletal pain. The expert sensory panel study showed that the sensations elicited by the prototype counterirritant patches were predominantly cooling, tingling, and low and short warming in nature, with strong adhesion, ease of application and removal, no staining, little to no residue and grease on the skin, and low lingering odor of menthol.

Conclusion: Literature search supports the use of counterirritants in the treatment of musculoskeletal pain like backache, strains, and sprains. In addition, the observations from the expert sensory panel study evaluating sensory and functional parameters of counterirritant patches showed that these patches provide predominantly cooling, tingling and low short lasting warming sensations with strong adhesion, no stain and little to no residue and grease. These results support their potential as a treatment modality with increased consumer acceptance, potentially increasing treatment adherence and maximizing the effectiveness of therapies. And may be used as part of multimodal pain treatment regimens for musculoskeletal conditions.

KEYWORDS: counterirritant, sensory panel, patches, capsaicin, menthol, salicylate, musculoskeletal pain

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INTRODUCTION

According to the World Health Organization (WHO), approximately 1.71 billion people had musculoskeletal conditions worldwide in 2019, and it is the leading contributor to disability [1]. Musculoskeletal conditions include conditions that affect muscles, bones, joints, and adjacent connective tissues leading to temporary or lifelong limitations in functioning, social participation, and mobility, affecting people's quality of life. These conditions are typically characterized by acute or chronic pain, which can be a symptom of a wide array of musculoskeletal disorders, ranging from acute injuries like ankle sprains to chronic conditions, including rheumatoid arthritis and osteoarthritis. The pain associated with musculoskeletal conditions is a common medical and socioeconomic problem worldwide [2]. Affected patients often seek medical attention, although many use non-prescription analgesics to facilitate self-care [3].

Pharmacological treatment of musculoskeletal pain is often multimodal and based on severity and duration of the pain. This ranges from oral medications, including acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), topical over the counter (OTC) preparations to weak and potent opioids [4]. Topical analgesics are an essential part of multimodal analgesia with the objective of attempting to block pain at peripheral sites, with maximum active drug and minimal systemic effects. Evidence based on empirical practice suggests that topically applied medications can be almost as effective as those taken orally, with a good safety profile. Moreover, improvement of patient compliance to medical treatment by providing effective pain relief with less central nervous system effects and minimal drug regimen burden further promotes the use of such topical preparations [5]. Treatment guidelines from various scientific societies and specialty groups also recommend using them earlier in the treatment regimen or even as the first-line treatment for mild-to-moderate musculoskeletal aches and pains [6] as a part of multimodal pain management. Most topical preparations are available as patches, ointments, or creams, and include a wide range of compounds that may have local analgesic, anaesthetic, or counterirritant effects.

Topical counterirritants provide a paradoxical pain-relieving effect by producing a less severe pain, hence masking a more intense one, i.e., they irritate the skin and create a temporary hot or cold sensation that can interrupt pain signals to the brain, essentially distracting the brain from pain. These counterirritants may provide mild-to-moderate pain relief but are not considered adequate for relieving severe pain. They are available in various over-the-counter (OTC) dosage formulations that may be either rubbed onto the skin (creams, foams, gels, lotions, and ointments) or made into patches or plasters that stick onto the skin [7]. Patients generally tend to accept patch formulations as familiar and convenient to use as these formats typically lack the undesirable characteristics of other topical formulations like malodorous, messy-to-handle creams and ointments [8]. Pain-relief patches also offer an advantage to those who require pain medication around the clock with multiple reapplications, which may significantly affect their quality of life. Salicylates, menthol, capsaicin, and camphor, in particular, are counterirritants commonly used as active compounds in the patches for managing musculoskeletal pain [9].

This article provides the background, current understanding, and therapeutic benefits of commonly used topical counterirritants in the management of acute and chronic musculoskeletal pain. In addition, as the sensory characteristics of these products can influence patient acceptance and usage in pain management to a great extent, this article also provides results of expert sensory panel study evaluating the sensory characteristics of counterirritant patches. Increasing the understanding of topical counterirritants may help or empower healthcare professionals to make the right decisions in the selection of topical products for pain management.

METHODOLOGY

PubMed, Google Scholar, and Cochrane Library databases were queried using the following search terms: "counterirritant," "rubefacient," "capsaicin," "nonivamide," "camphor," "salicylate," "glycol salicylate," "menthol," and "methyl nicotinate." Broader searches were also performed using the terms "topical," "patch," and "musculoskeletal pain" in title, abstract, and keywords. Details about an expert sensory panel study to evaluate the performance of various counterirritant containing patch prototypes were also collected.

RESULTS

History and development of counterirritants

Hot and cold treatments like cryotherapy have historically been used for the treatment of soft-tissue injuries and perhaps were the most common topical analgesic modalities. The benefits of using local heat and cold therapy to reduce pain from musculoskeletal injuries are very well recognized. Clinical evidence have shown that heat-wrap therapy provides short-term reductions in pain and disability in acute low back pain and provides significant pain relief of delayed-onset muscle soreness. Similarly the use of cryotherapy have shown positive effect on pain reduction and on the recovery of various sports injuries [10-12].

The Gate Control Theory, one of the well-accepted pain theories, explains how counterirritation and external sensations like cold can inhibit pain transmission. Each dorsal horn contains a 'gate' whose control depends on the relative activity of large-diameter (A-beta) fibers and small-diameter (A-delta and C-) fibers. Large-diameter (A-beta) fibers close the 'gate' by exciting inhibitory interneurons, thereby inhibiting pain. Conversely, small-diameter (A-delta and C-) fibers open the 'gate' by inhibiting inhibitory neurons and facilitating the transmission of noxious impulses, thereby

resulting in pain [13]. Sensations like cold or touch can inhibit pain transmission by causing stimulation of A-beta afferent nerve fibers. The increased firing rate of thermoreceptors within the cutaneous tissue may close the gate, blocking the input from the primary nociceptive afferents to the dorsal horn [14]. Through the perception of other sensations, counterirritants distract the person from the original pain produced by the injury and reduce the pain experience. (Figure 1)

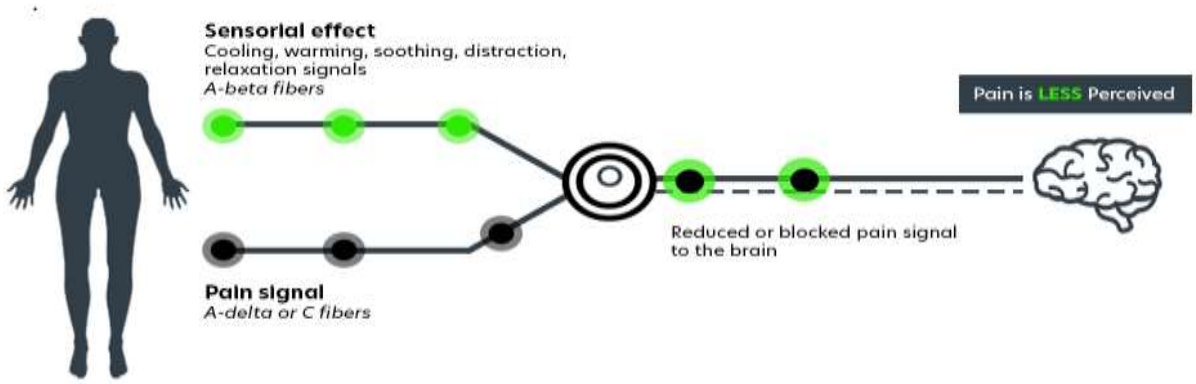

Figure 1. The brain can accommodate a limited number of signals, i.e. sensorial effect signals may get through the gate, reducing pain signals that can be transmitted to the brain

Classification of counterirritants:

Counterirritants are categorized into four groups based on their primary action: Group I agents include rubefacients like methyl salicylate; Group II agents, like menthol and camphor, primarily produce cooling sensation; Group III agents, like methyl nicotinate, cause vasodilation; and Group IV agents, like capsaicin, produce irritation without rubefaction [15].

Molecular mechanism of topical counterirritants

Evidence suggests that counterirritants, except those causing vasodilation like methyl nicotinate, initially excite and subsequently desensitize nociceptive sensory neurons by acting on the transient receptor potential (TRP) superfamily. These TRP receptors are thermosensitive – TRPV1 to TRPV4, TRPM2, TRPM4, and TRPM5 can sense hot or warm temperatures whereas TRPA1 and TRPM8 are activated by cold [16]. They can also detect changes in extracellular osmolarity or pressure, depletion of intracellular Ca^{2+} stores, acidic pH, and lipids. Activation of these TRP receptors by counterirritants initially produces local irritation and inflammation due to the release of calcitonin gene-related peptide, substance P, and other inflammatory neurotransmitters. However, their prolonged or repeated activation causes acute or functional desensitization to adapt to the irritation caused by the counterirritant. Acute or ‘‘pharmacologic’’ desensitization is characterized by a diminished response during a constant agonist application, while tachyphylaxis or ‘‘functional’’ desensitization is characterized by a reduction in response after many stimulations over a more extended period (Figure 2) [17]. Thus, the previously excited neuron becomes less responsive not only to the counterirritant but also to the original source of pain.

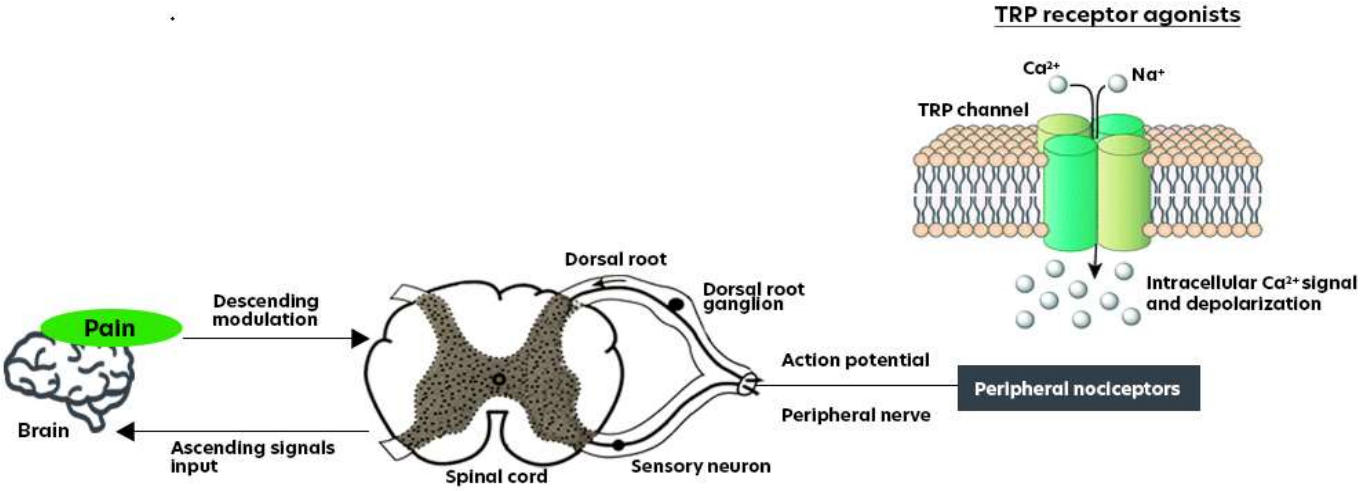

Figure 2: TRP receptor agonists cause calcium influx into the activated nerve cell, resulting in pain sensations. However, repeated application leads to persistent desensitization of these nociceptors, which ultimately reduces the transmission of painful stimuli through C-fiber conduction from the peripheral nerves to the central nervous system.

Commonly used counterirritants

Counterirritants causing irritation and warm sensation:

Capsaicin

Capsaicin, a natural alkaloid derived from red pepper (*Capsicum annuum*), has a long history of use for pain relief and is available in several OTC topical analgesics, usually at a concentration of <1%.

Capsaicin works by binding to nociceptors in the skin, specifically to the TRPV1 receptor, which regulates the movement of sodium and calcium ions across the cell membrane. Initially, the binding of capsaicin to nociceptors (TRPV1) produces itching, pricking, or burning sensations by inducing a sodium and calcium ions influx-dependent depolarization. Repeated applications or high concentrations give rise to a long-lasting effect, termed as 'defunctionalization,' leading to reversible degeneration of nerve terminals [18]. Products with a low concentration of capsaicin require multiple applications to provoke desensitization of nerves, which may be inconvenient for daily use. In addition, initial burning and pain on the application site may reduce patient adherence. Despite that, capsaicin is still considered an effective topical analgesic. In 2009, the US FDA and European Union approved the use of a capsaicin 8% patch under medical supervision for postherpetic neuralgia and non-diabetic neuropathic pain respectively [19].

Many OTC creams, lotions, and patches containing 0.025-0.075% capsaicin by weight are available for the management of musculoskeletal pain. European League Against Rheumatism (EULAR) also recommends capsaicin for musculoskeletal pain like osteoarthritis [20, 21]. A systematic review involving topical 0.025% capsaicin for the treatment of chronic musculoskeletal pain found a 38% mean response rate (percentage of patients with at least 50% pain relief) versus 25% for the placebo after four weeks of treatment; the relative benefit from topical 0.025% capsaicin compared with placebo was 1.5 [22]. Another systematic review describes that topical capsaicin (0.025%, 0.075%) was a better agent in pain relief than placebo (odds ratio, 4.36; 95% CI, 2.77-6.88); but its efficacy was moderate to poor in the treatment of chronic pain from musculoskeletal disorders [23]. A randomized, controlled, double-blinded study comparing the efficacy of topical capsaicin (0.05% cream) and topical NSAID (cream containing 5% ibuprofen) in acute musculoskeletal injuries reported a significantly higher clinical response in the topical capsaicin group without systemic side effects ($p = 0.001$) [24].

Nonivamide

Nonivamide, a structural analog of capsaicin, also acts as an agonist of human TRPV1 receptors and has been used in combination with other agents like nicoboxil-containing rubefacients to manage the discomfort in the musculoskeletal system.

A study reported that topical application of nicoboxil/nonivamide cream increased the concentration of oxygenated haemoglobin and tissue oxygen saturation in the skin and musculature below the treated skin area and thus may have beneficial effects in muscular complaints [25]. Additionally, many studies have confirmed the efficacy of a fixed-dose combination of topical nonivamide with nicoboxil in acute nonspecific low back [26, 27]. Furthermore, an observational study evaluating the effect of a nonivamide-based ointment as add-on therapy to systemic NSAIDs in patients with acute nonspecific musculoskeletal back pain showed an acceleration in the onset of the analgesic effect and discontinuation of systemic NSAIDs in 50% of patients after five days of use [28]. Another clinical study showed that 21-day topical nonivamide (0.01%) treatment had an analgesic effect in chronic low back pain [29]. Although evidence on the dermal sensitization potential of nonivamide is lacking, allergic reactions in humans following administration of capsaicin or capsicum extracts have been reported to be rare [30].

Counterirritants with rubefacient property:

Salicylates

Salicylates, including methyl salicylate and oil of wintergreen (a liquid form of methyl salicylate), are used in several OTC topical analgesic formulations. The Scottish Intercollegiate Guidelines Network (SIGN) also recommends topical rubefacients for chronic musculoskeletal pain [31].

The analgesic mechanism of topical rubefacients containing salicylates is not entirely understood. Preclinical data suggested that the level of COX inhibition associated with topically applied salicylates is as much as 100-fold lower than that for acetylsalicylic acid [11]. Thus, its believed that salicylates relieve pain in muscles, joints and tendons, and other musculoskeletal pains in the extremities by counterirritation (activation and desensitization of cutaneous nerves) [32]. In 2004, a systematic review of RCTs found that topically salicylates was significantly better in acute musculoskeletal pain reduction than the placebo group (relative benefit, 3.6; 95% CI, 2.4 to 5.6; NNT, 2.1; range, 1.7 to 2.8) [33]. In addition, studies on back pain revealed statistically significant pain relief with hydroxyethylsalicyclate (glycol salicylate) compared with placebo [34, 35]. Adverse events and long-term efficacy were reported to be poor for chronic musculoskeletal pain, but results from six double-blind, placebo-controlled trials indicated a relative benefit versus control of 1.5 (range, 1.3 to 1.9; NNT, 5.3; range, 3.6 to 10.2) [33]. Due to limited or insufficient data available, some uncertainty about the effects of salicylate-containing rubefacients remains [32].

Counterirritants inducing cooling sensation:

Menthol and Camphor

Menthol derived from plants in the Mentha genus and camphor derived from the camphor laurel tree are often used in topical analgesics, either alone or co-formulated with salicylates. FDA approves menthol for use as an external

analgesic in OTC medicines for human use when formulated at concentrations up to 16% [36].

Menthol activates transient receptor potential melastatin 8 (TRPM8), also known as cold- and menthol-sensitive receptors (CMR1) receptors, on the sensory nerves and vasculature. Topical applications have an initial cooling effect followed by a localized warming effect secondary to increased localized blood flow, and confer analgesia through its Ca^{2+} channel blocking activity [37]. In addition to activating TRPM8 receptors on sensory nerves, menthol binds k-opioid receptors and may thus confer an additional opioid analgesic effect [38]. Like capsaicin, camphor may produce its analgesic effect by activating and ultimately desensitizing the capsaicin receptor TRPV1 and TRPV3, as well as the garlic receptor, TRPA1 [39].

A systematic review assessing the clinical effectiveness of menthol-containing analgesic gel (with <5% topical menthol) for musculoskeletal pain found a significant reduction in pain [40]. In 2014, Sundstrup et al. evaluated the impact of 4% menthol gel on pain in slaughterhouse workers with carpal tunnel syndrome (CTS) and reported a 31% reduction in acute pain as compared to placebo [41]. The topical application of 5% menthol has also been reported to alleviate the severity and frequency of recurrence of musculoskeletal pain in hemodialysis patients [42]. Evidence also suggests menthol as a convenient alternative to cold therapies such as ice or cold packs. 3.5% topical menthol reduced the pain perception compared to ice (P = 0.02) in patients with induced muscle soreness [43].

Menthol is often combined with methyl salicylate to produce a counterirritant effect. A study investigating 6% menthol with 10% methyl salicylate and 3.1% camphor in patients with arthritic, neurologic, and musculoskeletal pain showed a significant reduction in Brief Pain Inventory (BPI) pain severity (49% vs 12%) and pain interference scores (58% vs 14%) when comparing the treatment and control group respectively [44]. Another study investigating 3% menthol with 10% methyl salicylate in patients with mild to moderate muscle strain showed a significantly greater pain relief (~40%) than a placebo patch (P = 0.005) [45].

Counterirritants causing vasodilation:

Methyl nicotinate

Methyl nicotinate, on application, readily penetrates human skin in vivo. Within minutes, it produces noticeable erythema and a transient increase in the skin perfusion through a vasodilatory response in the microcirculation. Its rubefacient effect is caused by a transient increase in the microcirculatory perfusion, which is hypothesized to be mediated through the prostaglandin D2 (PGD2) pathway. The mechanisms of action, however, have not been fully elucidated. Like most compounds that cause vasodilation, its vasodilatory effect is likely to be of multifactorial origin, including the release of nitric oxide (NO) from the endothelium, as well as neural effects [46].

An ointment formulation containing methyl nicotinate and glycol salicylate has been found to produce a highly significant linear regression of the pain symptomatology and a corresponding increase in athletic performance. The preparation's vasodilatory action produces greater muscular tissue tone and a definite reduction in crampiform symptomatology of athletes [47]. 1.2% methyl nicotinate in combination with other drugs like comfrey root extract has also been found to be effective in the treatment of acute upper or low back pain [48].

Various topical counterirritant formats

Patient preferences for a particular drug format may influence their compliance to the treatment; hence, it is important to understand this to achieve successful therapy outcomes [49]. Topical products work effectively on the superficial layers of the skin and exhibit the advantage of increased patient compliance due to simpler dosage regimens. Although topical products have a relatively better safety profile over systemic therapy, there are a few limitations, including patient variability in permeability of the skin, local skin irritation, and frequent mild, self-limiting skin adverse effects. Hence, patients must be counselled about their appropriate use [5].

Among all topical formats, patches offer advantages over other traditional topical formats like gels or creams, with more accurate dosing and continued delivery avoiding multiple applications per day. Table 1 summarizes the comparison between topical patches and gels and creams [50].

Table 1. Comparison of topical patches and other traditional topical formats, such as gels and creams

Parameters	Topical patches	Gels and creams
Visual appearance	Visible	Visible
Skin feel	Non-sticky, non-greasy	Sometimes sticky, greasy
Administration	Convenient	Sometimes messy
Dose adjustment	Low	High
Dosing frequency	1-7 days	1 day or less
Sustained release	Yes	No
Occlusive properties	Yes	No
Wipe off resistance	Yes	No
Residual remains	Possible	No

Counterirritant patches

Today, many OTC counterirritant patch formulations are available to provide symptomatic pain relief in various conditions such as muscle pain, strains, sprains, tendinitis, joint pain, and pain after sport injuries. Patients generally find these topical patches convenient to use, thus improve compliance over timed or scheduled dosing. However, there are certain characteristics and properties, including design, composition, or adhesion, that may affect the performance and safety of these OTC patches and impact patients' preference, acceptability, usability, and treatment adherence.

Adhesion is one of the critical attributes of the patches. Patches that lift up or fall off before the required time period of application may represent a therapeutic failure or suboptimal drug delivery and must be replaced [8]. Poor adhesion can also be a safety issue, as when patch systems fall off, there is the potential for accidental exposure to vulnerable others, including children or pets. Patch systems that adhere too well can tear off the skin and cause injury when they are removed. This can be a problem, particularly in elderly users, who tend to have frail skin with low moisture content and less elasticity. Skin irritation and sensitization to the administered adhesive substances of the patches can also pose challenge. Patients should be educated to properly use them and immediately seek evaluation by dermatologists in case of suspected skin reactions [51]. Regulatory agencies recommend evaluating the adhesion of topical delivery systems for Abbreviated New Drug Applications (ANDA) and recognize in vivo adhesion studies as one of the most meaningful predictors of commercial drug product performance [8, 52].

Similarly, sensory characteristics of counterirritant patches (e.g., cooling, warming, overall sensations, etc.), ease of application, odor intensity, staining during use, and after-feel attributes can affect patient preference or acceptance. These parameters, especially sensory parameters, can be analyzed through various methodologies including expert sensory panel studies, where different sensory characteristics are evaluated by a panel of trained experts, instead of instrumental or analytical tools. An expert sensory panel is typically composed of 10-15 carefully selected participants who are initially selected for their sensory acuity and articulacy, and trained to discriminate the different sensory attributes (e.g., aroma, warm/ cool intensity, etc.) across different products [53-55]. These expert sensory panel studies, along with consumer sensory studies, are vital for the deeper understanding of factors affecting consumer acceptance of such products [56]. Thus, sensory studies and a better understanding of these aspects may help to develop effective therapies and potentially improve treatment adherence.

Evaluation of sensory characteristics and functional parameters of pain-relieving patches: An expert sensory panel study

The objective of this study was to evaluate pain-relieving patches for their sensory characteristics such as overall sensation, cooling, warming, and tingling sensations, as well as functional parameters such as ease of application and removal, adhesive property, odor intensity, staining on clothes, residue or greasiness, and sweat/moistness on the skin after removal.

Expert Sensory Panel Study Methodology

Samples:

A total of five pain-relieving patches – two prototype patches formulated using the counterirritants menthol (Prototype A) and nonivamide (Prototype B), as well as three commercially available topical analgesic patches containing menthol, methyl salicylate, and capsicum extract as active ingredients (Marketed Products A, B, C) – were evaluated in the study to provide a precise description of the sensory characteristics associated with these ingredients.

These samples were evaluated in a sequential monadic manner using the Williams Latin Square Design as presented in Compusense SaaS ® (Compusense Inc., Guelph, ON, Canada) [57]. Patches were distributed in individual foil packets labelled with a 3-digit sample code and randomly assigned to participant's right or left shoulder for application.

Sensory panel:

An expert sensory panel comprising ten trained sensory experts evaluated the five patches. Each panellist evaluated one patch per day by applying it on their shoulders for up to 12 hours while measuring the various attributes using a 100-point intensity scale for quantitative profiling. The panellists alternated between the right and left shoulders and wore the same white shirt throughout the study, which was washed after every two patch evaluations. Panel evaluation was carried out in duplicate.

Test protocol:

First, the panel developed a lexicon to describe the key sensory differences among the patches as shown in (Table 2). Evolution of the overall sensation, cooling, warming, and tingling sensations were tracked concurrently over a 12-hour period on a 100-point intensity scale using multi-attribute time-intensity (MATI) method. This allowed for evaluation of more than one attribute over time compared to the traditional Time Intensity (TI) [58]. The panellists placed a patch on their shoulder and simultaneously clicked the start button of a timer. For each patch, the panellists evaluated the sensations for the first 5 minutes at 10 seconds intervals, then evaluated the evolution of the attributes after the first 5 minutes to the 30th minute at 5 minutes intervals, and finally for the rest of the 11.5 hours at 30 minutes intervals or when perception ended; which ever occurred first. The panellists scored whenever they noticed a change (decrease or increase) in the intensity of the attributes at the cued interval. They did

not touch the scale if they perceived no change in intensity and scored a zero and stopped the timer when perception ended. In addition to the MATI evaluation, the panellists also evaluated functional parameters namely patch adherence, presence of staining, ease of application and removal, residue and greasiness on skin, moistness or sweat on skin, and odor intensity on a 100-point at specific timepoints as shown in Table 2.

Table 2: Protocol and lexicon for the expert sensory panel study

	Attribute	Definition	Timeline	Low Anchor	High Anchor
Sensory parameters	Overall Sensation Intensity	Measure of the overall sensation, including cooling, warming and tingling sensations	Continuously for the first 5 minutes of application; then every 5 minutes for the first 30 minutes, and every 30 minutes thereafter	No Sensation	Very Intense
	Cooling Intensity	Measure of cooling sensation		No Sensation	Very Intense
	Warming Intensity	Measure of warming sensation		No Sensation	Very Intense
	Tingling/Biting Intensity	Measure of tingling/biting sensation		No Sensation	Very Intense
Functional parameters	Ease of application	How easy it is to apply the patch on the shoulder	At the 5-minute mark	Very Difficult	Very Easy
	Adherence	Percentage of the patch that is firmly adhered to the skin (capture visually)	Every 5 minutes for the first 30 minutes, and every 30 minutes thereafter	Completely Removed	Firm Adherence
	Odour Intensity	Measure of the odour intensity of the patch when applied	Every 5 minutes for the first 30 minutes, and every 30 minutes thereafter, then at removal (12 hours or earlier)	No Odour	Very Intense
	Staining on shirt	Presence of staining on white shirt at the location of the patch	Every 5 minutes for the first 30 minutes, and every 30 minutes thereafter, then at removal (12 hours, or earlier)	None	Very Stained
	Ease of removal	Ease of removal of the patch off the shoulder, peeling it from back to front	At removal (12 hours, or earlier)	Very Difficult	Very Easy
	Residue on skin	Amount of residue on skin after removal of the patch		None	Lots
	Greasiness on skin	Amount of grease on skin after removal of the patch		None	Very Greasy
	Sweat/Moistness on skin	Amount of sweat/moisture on skin after removal of the patch		None	Very Sweaty

The responses for the first 30 minutes were recorded on a computerized ballot; Compusense SaaS® on iPads (Compusense Inc., Guelph, ON, Canada). Panellists were prompted every 2.5 seconds for each attribute at the stipulated time interval to score the intensity of perception if any. For responses for the next 11.5 hours, panellists were asked to record their data on a sheet for convenience before transferring the data into Compusense. Panellists set up an alarm every 30 minutes and a reminder text was sent to them as well to prompt them to score the perception at a given time-point.

RESULTS

A) Evaluation of Sensory characteristics:

The formulations were evaluated for overall sensation, as well as cooling, warming, and tingling sensations.

Overall sensation

The overall sensations of both Prototypes A and B started quickly and by 80 seconds, intensity of sensations had reached the 10-point average intensity threshold. This was not significantly different from the commercial products tested, which started within 70 to 80 seconds and showed similar evolution of sensation. All the patches tested were thus relatively quick in providing their sensorial effects. Both prototypes A and B also provided long-lasting overall sensations of about 7.5 to 8.5 hours, not different from each other, while the other marketed products, the sensation lasted for 6.0 to 9.5 hours. Marketed Product B recorded the shortest and product C recorded the longest overall sensation among the tested products. (Figure 3, Table 3)

Cooling sensation

Prototype A started to deliver a cooling sensation at 80 seconds after application, reaching peak intensity at 10 minutes, and lasting 5.5 hours. Prototype B started to deliver a cooling sensation at the 110 seconds mark, reaching peak intensity at 15 minutes, and had the longest-lasting cooling effect for 7.5 hours out of all the products evaluated. Comparing the prototypes to the commercial products, the time cooling sensation ceases was not significantly different among the patches but relatively long-lasting (5.5 to 7.5 hours). (Figure 4, Table 3)

Warming sensation

The evolution of warming sensation for all tested patches began slowly (250 to 300 seconds), was of low intensity (less than 25 points), and lasted for about 25 minutes to 3.5 hours. The products only showed significant differentiation in peak intensities, where marketed Product C recorded the highest and Prototype B recorded the lowest. The two prototypes were not different from each other. (Figure 5, Table 3)

Tingling sensation

Tingling is another sensation perceived across the tested products; all tested products were primarily cooling and tingling in nature. For Prototype A, the perceived tingling sensation started at 2.5 minutes (150 seconds) and lasted for 3 hours, while for Prototype B, it started at 3.2 minutes (200 seconds) and lasted for 4 hours. The difference in intensity of tingling sensation between the prototypes and the commercial products were not significant; however, marketed Product C lingered the longest. Among the commercial products, marketed Products A and C provided longer tingling sensation which was at least 1.5 hours more than marketed Product B. (Figure 6, Table 3)

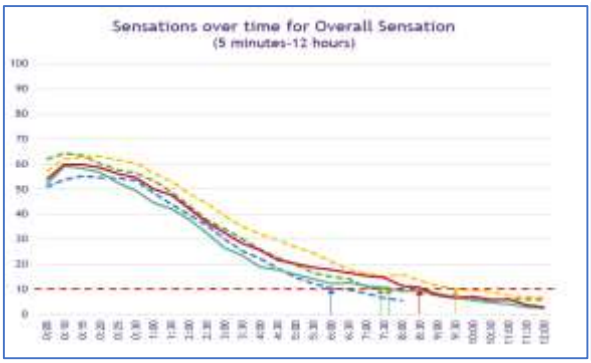

Figure 3: Overall Intensity Duration (last time point for which the score is >10 on a 100-pt scale)

Figure 4: Cooling Intensity Duration (last time point for which the score is >10 on a 100-pt scale)

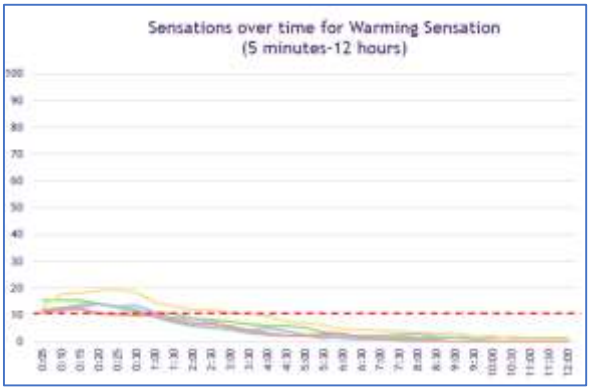

Figure 5: Warming Intensity Duration (last time point for which the score is >10 on a 100-pt scale)

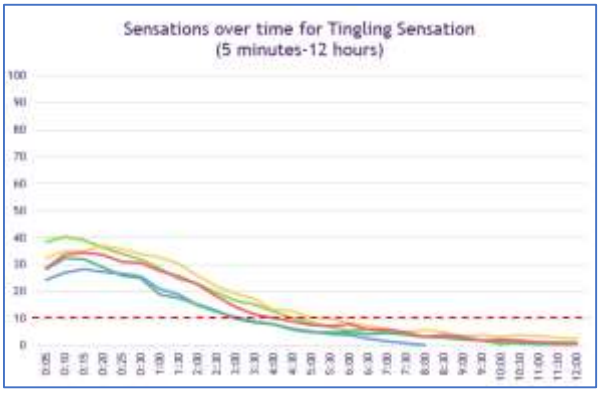

Figure 6: Tingling Intensity Duration (last time point for which the score is >10 on a 100-pt scale)

Intensity ratings for overall sensation, cooling, warming, and tingling sensations collected over 12 hours showed that both the prototype patches exhibited similar curves. The sensations increase rapidly for the first 10-15 minutes, then decrease over the next several hours. (Figure 7)

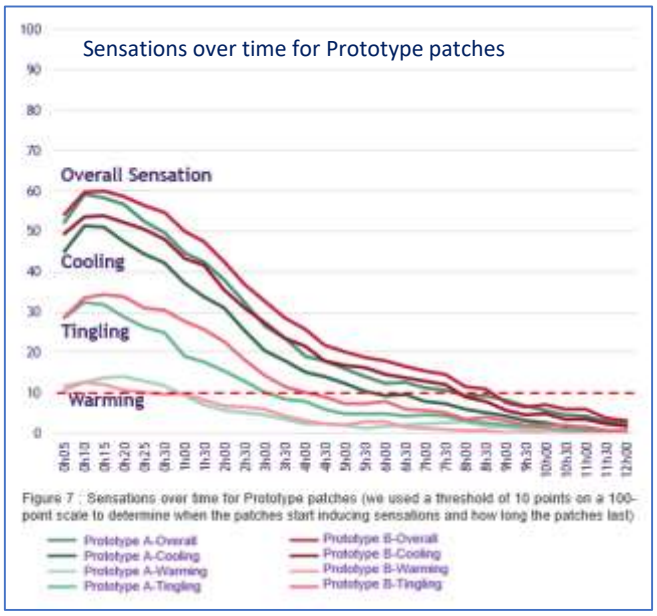

Figure 7 : Sensations over time for Prototype patches (we used a threshold of 10 points on a 100-point scale to determine when the patches start inducing sensations and how long the patches last)

Table 3: Summary of findings: Sensations over time for all the patches (Intensity start is the first time point for which the score is >10 on a 100-pt scale; Intensity duration is last time point for which the score is >10 on a 100-pt scale)

Sample tested	Overall Sensation Intensity		Cooling Intensity		Warming Intensity		Tingling/Biting Intensity	
	Overall Intensity Start	Overall Intensity Duration	Cooling Intensity Start	Cooling Intensity Duration	Warming Intensity Start	Warming Intensity Duration	Tingling Intensity Start	Tingling Intensity Duration
Prototype A	80 seconds	7.5 hours	80 seconds	5.5 hours	300 seconds	30 minutes	150 seconds	3.0 hours
Prototype B	80 seconds	8.5 hours	110 seconds	7.5 hours	300 seconds	25 minutes	200 seconds	4.0 hours
Marketed product A	70 seconds	7.5 hours	80 seconds	6.0 hours	250 seconds	30 minutes	100 seconds	4.5 hours
Marketed product B	70 seconds	6.0 hours	90 seconds	5.5 hours	300 seconds	1.5 hours	130 seconds	3.0 hours
Marketed product C	80 seconds	9.5 hours	90 seconds	6.5 hours	270 seconds	3.5 hours	150 seconds	5.0 hours

B) Evaluation of Functional parameters:

The formulations were further evaluated for adhesive property, staining, ease of application and removal, after-feel attributes, and odor intensity.

Patch adherence

Almost all the panellists reported that all the patches remained fully adhered for the whole duration of the study.

Presence of staining

Panellists wore white t-shirts to capture any staining from the patches. No staining was observed throughout the experiment for all the tested patches.

Ease of application and removal

The prototypes did not differ in the ease of application and removal, and were easier than marketed Product A and C. Marketed Product A was the hardest to apply and remove, and marketed Product B was easiest among all the patches. (Table 4)

Residue and greasiness on skin

All the patches left little residues and grease on the skin. There were no significant differences in residue or greasiness after removal between products. (Table 4)

Sweat and moistness on skin

All the patches produced varying degrees of moisture albeit low making them relatively breathable. Marketed Product A was the most breathable among all the patches evaluated.

Odor intensity

The study results showed that both prototypes had a medicinal odor that lingered less and was relatively less

intense than commercial products. All the patches had a characteristic menthol and camphor odor which progressively became weaker towards the end of the 12-hour study period. (Figure 8) The final odor intensity of the prototypes were not significantly different. There was no odor note present by at the end of the perception of overall, cooling, warming, and tingling sensations.

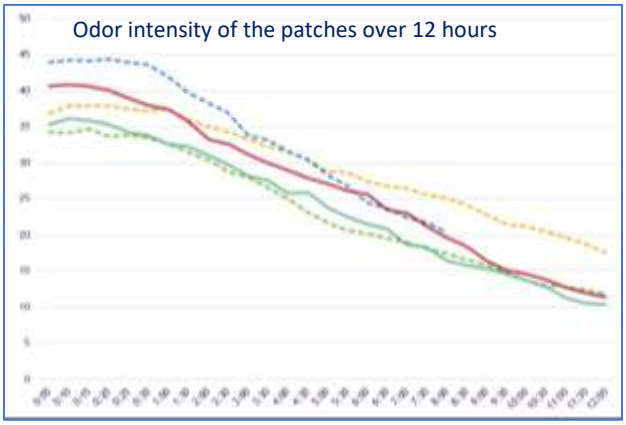

Figure 8: Evolution of odor intensity of the patches over 12 hours

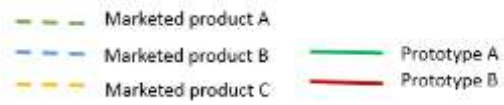

Table 4: Summary of findings: mean scores for ease of application and removal, and after-feel attributes

Sample tested	Ease of application	Ease of removal	Residue after removal	Greasiness after removal	Sweat/moistness after removal
Prototype A	76.1	79.5	13.0	6.2	12.2
Prototype B	74.2	78.1	12.2	6.1	19.5 (Most)
Marketed product A	41.0 (Hardest)	57.7 (Hardest)	13.3	6.7	1.7 (Least)
Marketed product B	87.0 (Easiest)	83.9 (Easiest)	11.1 (Least)	5.1 (Least)	12.0
Marketed product C	51.9	67.7	14.3 (Most)	10.0 (Most)	8.3

Overall, this expert sensory panel study showed that the sensations elicited by the prototype patches were characterized predominantly by cooling, tingling, and low and short warming sensations, with strong adhesion, ease of application and removal, no stain, little residue and grease on the skin, and low lingering odor of menthol.

CONCLUSION

Topical analgesics are emerging as a valuable multimodal analgesic treatment option in musculoskeletal pain conditions. Current literature supports the use of counterirritants in the treatment and management of musculoskeletal pain like backache, strains, and sprains. In addition, the observations from the expert sensory panel study evaluating sensory and functional parameters of counterirritant patches showed that these patches provide predominantly cooling, tingling, and low short lasting warming sensations with strong adhesion, no stain, little residue and grease, and low lingering odor. These results also support their potential as a treatment modality with increased consumer acceptance, potentially increasing treatment adherence and maximizing the effectiveness of therapies. Given that counterirritants have a good efficacy and safety profile with minimal local side effects, such medications should be used more extensively as part of multimodal pain treatment and management regimens for musculoskeletal conditions.

Clinical perspective for topical pain-relieving patches containing counterirritants

Topical analgesic agents have a definite role in acute and in some cases of chronic musculoskeletal pain. The main indications for these topical agents are in pain arising from large joints such as knee, hip, shoulder, and ankle joints. These agents are also popular for muscular pain due to

sprain and strains especially neck, and upper and lower back pain. The main criteria for health care practitioners to decide which agents to use depends on the following factors:

- Active ingredient
- Pharmacokinetics
- Onset and duration of action
- Odor, staining, and cosmetic issues
- Adhesive quality for topical patches
- Adverse effects to the skin such as skin irritation, redness and burning sensation.

The expert sensory panel study confirmed that the prototype patches (Prototype A and B) are promising candidates to fulfil these criteria. Based on their parity with the commonly available commercial agents, these prototype patches have the potential to be well accepted. Further research is needed to show the benefits of such topical patches in different age groups.

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CONFLICT OF INTEREST

Vandana Garg, Ramesh Agarwal, Katherine Mendoza, Rakesh Lalchandani and Zee Alcasid are all employees of Haleon (formerly GSK Consumer Healthcare).

AUTHOR CONTRIBUTION

All authors contributed to conceptualization, review and editing of the manuscript. All authors approved the final manuscript for submission.

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