WHAT IS KNOWN AND OBJECTIVE

Each of the major types of analgesic drugs (eg opioids, NSAIDs, paracetamol and pentanoids) has mechanism-associated adverse effect or abuse potential limitations. Thus, there is interest in discovering new agents that produce pain relief by alternative mechanistic pathways. Natural substances have been a rich source of compounds that possess analgesic properties and have spawned a variety of clinically useful synthetic analgesic drugs. Menthol has been used as a topical pain reliever since ancient times. Perhaps because of that, it is tempting to dismiss either its efficacy or its mechanism of action as trivial. However, recent advances in the (patho)physiology of pain have uncovered new pathways—one of which is responsible for the analgesic action of menthol. It is thus timely and important to review the basic science, clinical efficacy data and safety profile related to the pain-relieving attributes of menthol.
2 | METHODS

The PubMed database and Internet sources were searched using keywords related to menthol, analgesia, pain pathways, TRPM8, calcium channel, topical analgesic and others. The identified "hits" were initially limited to clinical trials and reviews published in the past 5 years, which yielded 31 results, and relevant basic science studies published in any year. Articles not available in English or about the oral route of menthol were excluded. The bibliographies of the included articles were used for identification of supporting articles. The articles could be grouped under the main topics of transient receptor potentials, the mechanism of action of menthol, its cooling effects and clinical applications of topical menthol. These sources, plus the collective expertise and experience of the authors, formed the basis of this narrative review.

3 | RESULTS

3.1 | Basic science

Menthol (also "mint camphor"), is a volatile oil extract derived from the genus Mentha (mint), is widely available in natural and synthetic forms. A cyclic terpene alcohol, menthol, acts on the transient receptor potential melastatin-8 (TRPM8) receptor.\(^2\) Menthol is also a vasoactive agent that produces cutaneous vasodilation.\(^3\) It has been extensively used in both effects traditional medicine. Applied to the skin, it imparts a cooling effect and might also act as a weak sodium channel blocker.\(^5\) Its action on activity-dependent voltage-gated neuron channels confers to it a weak, localized anaesthetic effect.\(^6,7\) At low concentrations (<1%), menthol depresses cutaneous nociception and may even desensitize nociceptive C-afferent fibres\(^8\) but at high concentrations (>30%), menthol is irritating.\(^9\)

Menthol is a cyclic terpene alcohol with three asymmetric carbon atoms. There are four pairs of optical isomers: (+)- and (−)-menthol, neomenthol, isomenthol and neoisomenthol. The analgesic properties of menthol are thought to be attributable primarily to the (−)-menthol isomer (Figure 1).\(^10\) Menthol produces its topical analgesic action\(^2\) through an interaction with the dense network of nerves that are embedded in the skin's dermal-epidermal junction. The nerves project fibrous strands through the epidermis very close to the skin's surface. The nerve endings detect cutaneous stimulation, activate inflammatory responses, release vasoactive neuropeptides and send pain signals. Among the nerves are unmyelinated C-afferent fibres, which conduct slowly, and myelinated A-afferent (including A-δ) fibres, which have a variety of diameters and conduct more quickly. Most of the rapidly conducting A-afferent fibres have no myelin sheath at or near the skin’s surface, which makes them extremely sensitive to thermal, chemical and physical stimuli.\(^11\) Upon stimulation, unmyelinated termini send neural impulses that allow for precisely timed opening of voltage-gated ion channels so that sodium, potassium, chloride and calcium ions are allowed inflow and outflow through the membrane of the neuron. (Neural membrane excitability is governed by other factors as well, including transient receptor potential channels and others.) Thus, the surface of the skin is extremely sensitive to even mild stimulation.

Signal transduction is mediated by substances that are produced by cutaneous cells such as keratinocytes. After injury, neuropeptides and noradrenaline released from nerve terminals in the skin activate receptors on the surface of keratinocytes, which in turn leads to the production of inflammatory cytokines and nerve growth factor (NGF), which in turn degranulate mast cells and increase the sensitivity of cutaneous nociceptive neurons, thus increasing pain intensity.\(^12,13\) It is thought that topical agents that can penetrate the stratum corneum (the outermost cutaneous layer) may be able to modify this series of events. The stratum corneum is composed of

![FIGURE 1](Image from Wikimedia Commons)
multiple layers of dead, hydrated corneocytes surrounded by a lipid matrix in a way described as "brick-and-mortar." The stratum corneum varies in thickness at various parts of the body and is perforated by hair follicles and sweat glands. A healthy individual with a robust immune system has a vigilant and effective protective system to attack and neutralize invaders that penetrate this layer.

3.2 | The role of the transient receptor potential (TRP) in pain perception and analgesia

Transient receptor potential melastatin-8 (TRPM8) has been nicknamed the menthol receptor. TRPM8 is activated by temperatures below 26°C as well as by a variety of chemical agents (Figure 2A-D), including menthol, cumbelin (a sesquiterpene alcohol) and icilin (a synthetic TRPM8 agonist). TRPM8 is part of a larger family of TRPs. The transient receptor potential vanilloid type I (TRPV1) was first elucidated in the 1990s; TRPV1 is the receptor activated by capsaicin, the active ingredient of hot pepper. At least six subfamilies of transient receptor potentials have now been identified: vanilloid (TRPV), canonical (TRPC), melastatin (TRPM), ankyrin (TRPA), polycystin (TRPP) and mucolipin (TRPML), along with 28 associated gene products. All of these are non-selective cation channels at the nerve endings or along the axons of neurons involved in pain sensation or perception. Their role is to transduce a range of stimuli, including (but not limited to) temperature. The channels promote the propagation of action potentials which travel via the spinal cord to brain pain processing centres.

In broad terms, the TRP ion channel family in mammals senses temperature; TRPM8 (along with TRPA1) specifically senses cold. Human thermoregulation is relayed mainly by the sensory neurons of the dorsal root ganglia. Neural information is transmitted to the brain, where it is integrated in the hypothalamus, which actuates the peripheral autonomic system to regulate temperature by adjusting cutaneous blood circulation. Peripheral sympathetic neurons also play a key role in cold-sensing, although they lack TRPA1 and TRPM8 channels. Recent research indicates that different fibres located in the peripheral sympathetic nervous system may release transmitters directly when they are cold, which might offer an explanation for peripheral blood circulation failure at low temperatures. The number of exocytotic vesicles increases significantly when exposed to low temperatures, at least in vitro. It is known that PC12 cells (derived from a pheochromocytoma of the rat adrenal medulla) and sympathetic neurons do not express the typical cold-sensing channels (TRPM8 and TRPA1), which suggests that the body possesses another cold-detection system that reacts to low temperatures by emitting transmitters via exocytosis, which in turn regulate peripheral circulation. The main thermoreceptor for both cellular and behavioural response to the cold is the non-selective ion channel TRPM8, which possesses the unique attribute of perceiving a broad range of temperature sensations, ranging from pleasant temperatures.

**FIGURE 2** A simplified illustration of the structure and functionality of TRPM8. (A) The five membrane-spanning regions and ion pore of TRPM8. Activation by temperature (B), specific chemicals (C) or KCl (D) results in Ca²⁺ transients in DRG (dorsal root ganglion) neurons. (B) to (D) from Caspani et al. (2009)
to painful. TRPM8 provides the broadest and most nuanced type of temperature sensing yet elucidated. TRPM8 is also responsive to cooling agents, including menthol.

Peripheral thermoreceptors sense cooling of the body when TRPM8 is activated by menthol. TRPM8 is activated by mild cooling and when activated depolarizes sensory neurons. More intensive cooling activates TRPA1, which is associated with cold pain. TRPM8 appears to be adaptive to variations in temperature over the long term and is sufficiently sensitive to detect even small fluctuations in temperature. In mammals, the response to cooling depends on the intensity and duration: short mild cooling may be perceived as pleasant, whereas more cold is uncomfortable, and freezing sensations are severely painful, even producing a paradoxical burning-like sensation. The extremely low temperatures that cause skin to freeze are perceived as severely painful by all nociceptors. Gentle cooling is perceived by fewer nociceptors, limited to those that have specific cold sensors, which may help explain why it is felt as mild and even pleasant. In clinical trials of analgesics, the surrogate model of cold pain is sometimes used in that it can be readily induced and serves as a valuable tool to help assess analgesic response. High-concentration topical menthol consistently induces cold hypersensitivity in humans and can thus act as a good model for cold hyperalgesia. Interestingly, experiments suggest that cold pain can be induced in healthy humans at temperatures within the moderate range. A6 fibres appear to regulate (inhibit) cold nociceptive input; blocking these fibres may result in pain.

TRP channels play roles in multiple conditions, including cold perception. The activation of TRPM8 by chemical agonists (such as menthol which cross-activates TRPA1) produces analgesia in neuropathic rats. Neuropathic pain may be particularly responsive to TRPM8 in that neuropathy is characterized in part by thermal hypersensitivity. Paradoxically, TRPM8 can produce cold hyperalgesia or it may relieve it. Menthol is a selective activator of TRPM8 channels. TRPM8 channels are expressed in a subset of the sensory neurons of the dorsal root ganglion and the trigeminal ganglia. It appears that topically applied menthol may also activate higher central analgesic pathways. In a preclinical study, TRPM8 activation via topical menthol was able to reduce hypersensitivity caused by nerve injury. This analgesia is not reversed by naloxone, indicating that opioid receptors are not involved.

The ability to sense cold is crucial to the body’s thermoregulation and defense systems, but also contributes to alldynia and hyperalgesia associated with cold. When the cold-sensing system is impaired, it can contribute to any number of painful conditions, including neuropathic pain, complex regional pain syndrome and chemotherapy-induced alldynia.

3.3 Topical menthol’s mechanisms of action

Menthol, along with other substances such as capsaicin and camphor, are counter-irritants. They first activate nociceptors on the skin (which is why they are sometimes used to act as surrogates for pain in clinical trials) and then desensitize them. Menthol is also a vasodilator; however, the exact mechanism by which this is mediated remains unclear. It has been suggested (but not universally endorsed) that menthol acts as a vasorelaxant. Differences in findings may be due to species differences or in the vascular beds of test subjects. In a study of ten healthy adult volunteers, menthol produced significant vasodilation vs baseline at all concentrations of 100 mM menthol or greater, and cutaneous vascular circulation was attenuated at all application sites compared to controls. This vasodilation increased in dose-dependent fashion. Inhibitors (lidocaine, among others) could effectively block menthol-related vasodilation. The sensations associated with topical menthol were significant at five minutes to 60 minutes after application compared to baseline. Cutaneous vasodilation with menthol could be measured at 15 minutes after menthol application and remained elevated up to 45 minutes after application, but returned to baseline at 60 minutes.

3.4 Clinical profile: the cooling effects of menthol

In a study of 10 healthy male volunteers (age 25-30 years), menthol was applied topically in three concentrations (0.5%, 4.6% and 10.0%) in random sequence to the left thigh to measure skin-cooling effects using a digital infrared camera as well as self-reports on a visual analogue scale. All three concentrations significantly decreased skin temperature compared to baseline for at least one hour (P < 0.05). The cooling effect was significantly more pronounced with the 4.6% concentration than the weaker (0.5%) or stronger (10.0%) concentration. Thus, while menthol has a demonstrable cooling effect on the skin, it is not proportional to the concentration of menthol.

Like ice or cold packs, menthol gel decreases arterial blood flow. In a clinical study of 19 healthy volunteers (mean age 26 years), four treatments were randomly applied for 20 minutes to the right forearm on four different days (at least 24 hours apart): 3.5 mL menthol gel, 0.5 kg crushed ice, 3.5 mL menthol gel and 0.5 kg crushed ice, and no treatment (control). Radial artery blood flow significantly decreased compared to baseline with ice (~20% to ~24%), menthol (~17% to ~24%) and ice plus menthol (~36% to ~39%), but not in the control group (3% to 9%). Menthol was associated with significantly less discomfort than the ice at 5, 10 and 20 minutes following application (P < 0.05). There were no observed changes in arterial diameter or heart rate.

Application of high concentrations of topical menthol was explored in a study to find a human surrogate pain model. Cold hyperalgesia could be reliably reproduced in human subjects over a one-week observation period using topical menthol. As cold hyperalgesia and cold allodynia can be features of neuropathic pain syndromes, the use of high-concentration menthol can be a valuable proxy for studies of such complex conditions as polyneuropathy.

3.5 Clinical profile: the role of topical menthol in the treatment of specific painful conditions

Topical products containing menthol are used in patients with a wide range of conditions, including the management of pain associated...
with muscle strain, back pain, joint pain, arthritis-related painful conditions and so on. These products offer both a cooling sensation, which can offer comfort, and pain relief.

### 3.5.1 Alldynia

Thermal and mechanical hyperalgesia are prominent features of inflammatory pain and neuropathic pain, and may be affected by peripheral or central sensitization, leading to chronic pain (chronification). A noxious stimulus prompts release of pro-inflammatory mediators that activate nociceptive processes that, in turn, become sensitized. For example, sensitized nociceptors have a lower threshold for activation (in other words, lower the pain threshold).  

### 3.5.2 Migraine

Migraine headaches are prevalent and represent a common type of neurovascular disorder. A genetic component of migraine has been hypothesized and may involve TRPM8. TRPM8 may be expressed in the sensory afferents associated with the meninges which may contribute to migraine. Exogenous activation of meningeal TRPM8 has been shown in preclinical studies to both cause and alleviate headache-related behaviours. In humans, it has been observed that cold can trigger a migraine but, alternately, the cooling action of menthol can alleviate headache pain. Thus, TRPM8 may be considered a potential target for personalized medicine or migraine therapy, and the role of menthol may be important.

#### 3.5.3 Musculoskeletal pain

In a study of 66 adults suffering from musculoskeletal pain, a topical product containing essential oxygen oil (oxygenated glycerol triesters [OGTs]) with menthol provided significantly better pain control at 8 days than did mentholated cream alone in a randomized, double-blind, single-centre study (P = .016). A randomized study compared 3.5% topical menthol to ice on the non-dominant elbow flexors in 16 volunteers who 2 days earlier had carried out specific exercises aimed at inducing muscle soreness. Maximum voluntary contractions, which evoked tonic contractions of the muscles were evaluated at baseline (T1), 2 days after the exercises, and 20 (T2), 25 (T3) and 35 minutes (T4) after application of menthol or ice. Pain was assessed on a 10-point visual analogue scale. Pain perception at T2 was significantly lower with topical menthol than ice (P = .02), and tetanic force was significantly greater (117%) with the topical analgesic than with ice.

Menthol applied to the skin in the region of the right and left popliteal arteries was evaluated in 16 healthy adult volunteers following isokinetic knee exercises (extension-flexion). Patients in this study were randomized to receive either menthol gel 3.5%, menthol wipe 10% or placebo. Blood flow was assessed five minutes following treatment application on both right and left arteries; this procedure was carried out once a week until each volunteer had been exposed to each of the treatments. Both menthol products resulted in a significant decrease in popliteal blood flow on the right (−19.60% to −8.39%) and left (−14.72% to −5.4%) sides, but the placebo treatment resulted in a bilateral increase (26.40% to 15.19%). The right popliteal artery also had a significant decrease in diameter with both menthol doses (−5.73% to −6.73%) but not with the control treatment (+6.67%). Thus, menthol used topically can rapidly reduce ipsilateral and contralateral arterial blood flow and ipsilateral arterial diameter.

### 3.5.4 Neuropathy

Neuropathic pain can be particularly challenging to treat as it involves aberrant neural signalling. Topical treatments such as capsaicin have been effective in treating certain neuropathic painful conditions. TRPM8 agonists, including menthol, may also be useful agents in the treatment of neuropathic pain. Cold allodynia is a prominent and particularly distressing feature of many forms of neuropathic pain. Topical menthol has been shown to help relieve the pain associated with chemotherapy-induced peripheral neuropathy (patients in this study had either chemotherapy-induced peripheral neuropathy or post-mastectomy pain syndrome). In an open-label "proof of concept" study of 51 cancer patients with problematic treatment-related neuropathic pain (median age 61 years, range 20-89 years), the painful area was treated with topical 1% menthol cream twice daily over 6 weeks with assessments at four and 6 weeks. A significant improvement in the total Brief Pain Inventory score (median 47-34, P < .001) was observed at 6 weeks, as were improvements in mood (P = .0004), catastrophizing (P = .001), functional ability to walk (P = .008) and sensation (P < .01). In this study, 50% of patients might be classified as responders in that they had a clinically meaningful reduction in their pain intensity of ≤30%. Furthermore, effect onset was rapid, and no dose titration was necessary.

### 3.5.5 Sports injuries

In a clinical study, healthy participants (N = 19) were randomly treated with an application of four different substances on the right forearm for 20 minutes: (i) 3.5 mL menthol gel; (ii) 0.5 kg crushed ice; (iii) 3.5 mL menthol gel plus 0.5 kg crushed ice; (iv) no treatment. Right radial artery diameter (cm) and blood flow (mL/min) were measured every five minutes during the treatment phase, and discomfort was assessed on a 10-point analogue scale with 10 the worst discomfort imaginable. Compared to baseline measure, radial artery blood flow decreased significantly (P < .05) with ice (−20% to −24%), menthol gel (−17% to −24%) and ice/menthol combined (−36% to −39%), but not for controls (3% to 9%). At 20 minutes, only ice (−27%) and ice plus menthol (−38%) produced significantly reduced blood flow (P < .05). Discomfort was significantly less with menthol gel than with any treatment using ice. No changes in heart rate or in arterial diameter were noted.

In another study of 17 healthy adults, menthol gel significantly reduced blood flow to the radial artery at 5 minutes (−42%, P < .05 compared to baseline), but the decrease was not significant at 10, 15 or 20 minutes of application.
Thus, menthol has a fast-acting but also short-lived effect on reducing blood flow.

4 | WHAT IS NEW AND CONCLUSIONS

Pain control is a difficult challenge for medicine. Each of the major oral analgesic agents has inherent drawbacks related to adverse effects or abuse potential. Topical analgesics deliver the active agent locally rather than systemically, which may improve tolerability and reduce the risk of drug-drug interactions. Patients tend to accept these products as familiar and convenient, and their role is likely to increase as the ageing population seeks to manage painful symptoms without using difficult-to-swallow oral agents or opioids. Menthol has a long history of use as a topical analgesic. Recent elucidation of TRPM8 channels as the “menthol receptor” has provided a rational and evidence-based mechanism of analgesic action. Clinical studies have reported that topical menthol appears safe and effective in treating a variety of painful conditions, including musculoskeletal pain, sports injuries, neuropathic pain and migraine.

An important potential application of topical analgesics is in multimodal pain therapy. Patients who must deal with persistent pain may find that topical pain relievers in conjunction with other interventions might provide better pain control than when they are used individually. Thus, even among patients who may be using other pain control strategies, topical analgesics may still play an important adjunctive role.

The modern understanding of menthol’s pharmacologic mechanism of action (TRPM8 channels) may lead to an expanded role for this substance in the search for replacements for opioid analgesics. It might also serve as a template for discovery of novel non-opioid analgesics.

POTENTIAL CONFLICT OF INTEREST STATEMENT

Dr Pergolizzi has a financial interest in a menthol-containing product (OxyRub), but this article was prepared independently. Dr Raffa, Dr Taylor and Ms LeQuang have no conflicts of interest.

ORCID

J. V. Pergolizzi http://orcid.org/0000-0001-5658-1471
R. Taylor http://orcid.org/0000-0001-5971-361X
J.-A. LeQuang http://orcid.org/0000-0003-4794-0318
R. B. Raffa http://orcid.org/0000-0002-1456-4451

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