Capsaicin and Menthol: A Comparison of Treatments for Diabetic Neuropathy

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Abstract

As diabetes rates rise, so do rates of peripheral neuropathy, a painful condition caused by damaged or overactive nerves which is commonly a symptom of diabetes. Capsaicin is commonly prescribed to patients with peripheral neuropathy as it alleviates pain by the activation of Transient Receptor Potential Cation V1 (TRPV1), which desensitizes nerves. However, this treatment contaminates the air and surrounding environment and is accompanied with a burning sensation, leading to poor patient compliance. Therefore, this paper investigated the pain mechanisms of Transient Receptor Potential Cation Channel M8 (TRPM8) and TRPV1, along with their main agonists menthol and capsaicin respectively to find out if menthol could be used to treat diabetic peripheral neuropathic pain and serve as an alternative to capsaicin. This paper looked at articles investigating the causes of various symptoms of peripheral neuropathy, the mechanism of action and side effects for capsaicin, the supposed central and peripheral mechanisms of action for menthol, along with articles investigating possible side effects, complications, and cost effectiveness of menthol. These scholarly articles demonstrated menthol could have similar mechanisms of actions to capsaicin with fewer side effects and lower cost. Unlike capsaicin, menthol could also have mechanisms of action in the CNS, therefore being more effective. The body of research indicates that menthol could treat diabetic neuropathy and be a more potent alternative to capsaicin. However, clinical trials and comparisons using menthol have not been conducted on humans. This paper advocate for Phase 1 clinical trials and trials on humans to investigate the supposed increased effectiveness as a treatment for diabetic neuropathy

The Use of Capsaicin and Menthol to Relieve Diabetic Peripheral Neuropathy

Introduction

Peripheral neuropathy is often a symptom of diabetes, causing shooting and stabbing pains, along with warped sensations. According to Pinzur (2011) in a review of diabetic peripheral neuropathy, "diabetic peripheral neuropathy likely affects up to one-third of adults with diabetes. All diabetic patients are likely to develop peripheral neuropathy if they live sufficiently long" (p.348). Furthermore, Pinzur describes diabetic peripheral neuropathy as "the most destructive type of form of peripheral neuropathy encountered by the orthopedic surgeon" (p.345). This statement is supported by the Capsaicin Study Group (1991), which claims "pain is commonly associated with diabetic neuropathy" (p.2225). In his review of literature relating to neuropathic pain, Baron (2005) agreed, elaborating the necessity of treating chronic conditions characterized by nerve damage, e.g. diabetic neuropathy, stating "pain becomes the primary concern rather than a symptom" in these cases (p.5). Baron also elaborated on the pain felt in these chronic conditions, ranging from shooting pains (p.100) to heat allodynia (p.97), in his assessment and analysis of peripheral neuropathy symptoms.

Within this analysis, Baron attributes pain felt in chronic conditions to functional

changes in the surface proteins of nerves, caused primarily by nerve damage. Facer et al., (2010) agreed, and investigated the change in surface proteins by quantifying the change in thermo-TRPs. Facer et al. researched this change by taking samples of nerves from various patients with nerve damage and performing an immunoassay for thermoTRPs on the nerve surface. However, in all sources, it is accepted that diabetes causes painful peripheral neuropathy which does not fade. Therefore, a common treatment is capsaicin, a TRPV1 agonist that defunctionalizes nociceptive fibers. A prospectively more effective alternative is menthol, a TRPM8 agonist which could be more effective with less drawbacks than capsaicin. This increased effectiveness would be due to the fact menthol provides analgesia in diabetic neuropathy through peripheral mechanisms, like in capsaicin, and central mechanisms as well. Therefore, further investigation, such as a clinical trial, is justified.

The Desensitization of Nociceptive Fibers by Capsaicin

The oldest mechanism for capsaicin analgesia is the desensitization of nociceptive fibers. Szallasi, Franscisco, and Geppetti (2006) stated that capsaicin activates TRPV1 whose initial excitation lead to "a durable refractory state during which previously excited neurons are unresponsive to a broad range of unrelated stimuli" (p.545). One common explanation of this refractory state is the depletion of substance P from nociceptive nerves. This explanation is referenced in The Capsaicin Study Group's (1991) clinical trial of capsaicin on diabetic neuropathy, which claims "capsaicin causes substance P, a pain-modulating neurotransmitter, to be depleted from small unmyelinated sensory neurons and their terminals" (p.2228).

This explanation is yet again addressed by Anand and Bley (2011), who, in their investigation of topical capsaicin for pain management, specifically the investigation of the therapeutic potential and mechanisms of action of a new high-concentration capsaicin 8% patch, find this mechanism of action erroneous. Anand and Bley agreed that the activation of TRPV1 by capsaicin causes desensitization, or defunctionalization as they call it, of nociceptive fibers, though they claim that capsaicin competitively inhibits the Electron Transport Chain (p.493). Anand and Bley also noted that TRPV1 is extremely permeable to calcium, with an 8:1 ratio of calcium to sodium in the beginning which can become 25:1 when activated by capsaicin, displaying that huge amounts of calcium enter the cell and is expressed on the ER, causing more calcium to be released (p.492). Anand and Bley claimed that the activation of TRPV1 and subsequent inundation of calcium causes osmotic swelling of the cell and activates proteases, which, in combination with the inhibition of the ETC, causes the defunctionalization of neurons (p.493). Anand and Bley explained the loss of Substance P as the loss of a marker associated with fibers, which may die out without energy from the mitochondria (p.494).
This side effect of capsaicin therapy, the potential death of fibers, is troubling, as it may lead to a general loss of sensation. This loss of feeling would lead to the inability to feel heat or acidity, decreasing the quality of life of capsaicin users. Beyond that, the potential loss of feeling, specifically pain, could lead to the inadequate avoidance of pain. A more troubling complication is the loss of C fibers, which may interact with blood flow and wound repair, besides pain sensation (Anand and Bley 2011, p.498). However, these side effects have not yet been seen (Anand and Bley 2011, p.498).

Yet, capsaicin has other, less severe complications as well. One major issue with capsaicin use is the contamination of the environment, as capsaicin cream can get on clothes, tables, and various other parts of the environment. This contamination of the environment can irritate the respiratory tract by inhalation and cause a burning sensation on the skin even when not applied (Anand and Bley 2011, p.491). Capsaicin also irritates the olfactory bulb by activating

TRPV1 (Szallasi et al. 2006, p.546). For capsaicin cream, the irritation of the olfactory bulb means that treatment with capsaicin can burn the nose without application due to the contamination of the environment. Capsaicin cream that has contaminated clothes can burn the patient and others around them, when put in contact with the clothing. These problems generally lead to a low patient compliance, indicating that a milder alternative may be of use.

Menthol Analgesia

It is known that menthol causes analgesia. This was seen by Klein et al., (2010), who topically applied l-menthol to rats, which induced heat analgesia and mechanical allodynia, leading Klein et al. to state that "menthol increased paw withdrawal latencies to noxious heat in a concentration-dependent manner, indicating an antinociceptive effect. The highest menthol concentration also significantly increased cold plate latencies, consistent with antinociception" (p.182). This application of l-menthol also had a biphasic effect on cold sensitivity (Klein et al. 2010, p.182). The validity of menthol analgesia was supported by Proudfoot et al., (2006), who applied icilin and menthol to rats, primarily to study whether menthol analgesia could be mediated by the TRPM8 cold receptor for chronic neuropathic pain, using a condition (CCI) similar to diabetic neuropathy.

Proudfoot et al. noted that menthol caused a nociceptive effect in rats, however this was specific to higher concentrations (p.1592). The usage and analgesia in higher concentrations in rats indicates that a relatively high concentration of menthol is needed for nociception in humans. There is also an issue of penetrating skin, though this can be done with the right vehicle, such as Tween or ethanol. Similar to capsaicin, menthol's nociception cannot be explained by anesthesia, indicating that both effect pain transmissions as compared to blocking all signals (Klein et al. 2010, p.182). This specificity allows for its use in peripheral neuropathy and diabetic neuropathy, as it does not hinder sensation beyond pain transmission. The use of high concentrations indicate that menthol is safe to use on humans, but the most effective concentration is unknown. However, to find the most effective concentration, large studies on humans or Phase 1 clinical trials must be done. Variation by patient would make these studies difficult, as diabetic neuropathy varies in intensity and location for each patient.

The idea of menthol analgesia is also supported by Pan et al., (2012) in "Central Mechanisms of Menthol-Induced Analgesia", which proposed numerous central and peripheral mechanisms of menthol analgesia. Pan et al. also used the formalin test to test the type of analgesia, peripheral or central. The formalin test could test whether capsaicin has a central mechanism of action, though all of the data suggests otherwise. Therefore, more research on the formalin test's effects with capsaicin should be done. With defunctionalization as the mechanism of action for capsaicin, it would alleviate the first phase of formalin, though it is in question if capsaicin would pass the second phase of formalin. If capsaicin does not, menthol appears to, indicating it may be far more effective than capsaicin generally in alleviating diabetic neuropathic pain (Pan et al. 2012, p.664). If menthol has an effective central mechanism of action, injecting menthol into the CNS may be a more selective way of alleviating CNS pain, or generally blocking pain. Interestingly, Proudfoot et al. (2006) also demonstrated that menthol can provide analgesia intrathecally as well as topically (p.1601), further demonstrating menthol's peripheral and central effects. Patel, Ishiuji, and Yosipovitch (2007) also noted that "similar to capsaicin, menthol may also cause analgesia by desensitizing nociceptive C fibres" in their paper on the various uses and effects of menthol (p.3).

It must be noted that Brederson, Kym, and Szallasi (2014) state that "a second study (Caspani et al., 2009) was unable to replicate this finding" in their review of literature related

to thermoTRPs (p. 69). And, although menthol analgesia is also supported by Macpherson et al., (2006) in their investigation of the specificity of thermoTRP agonists, found through electrophysiology, they noted that "the mechanisms of [menthol's] anti-pain actions are unclear" (p.336). Macpherson et al. went on to further state "the cooling sensation of menthol could distract us from pain; alternatively, it could block the activity of a pain-sensing molecule" (p.336). Should the mechanism of action of menthol be distraction, menthol would be a far worse analgesic than capsaicin for more than just diabetic neuropathy. However, this does not seem the case with menthol, as so many peripheral and central mechanisms of actions have been proposed.

Peripheral Mechanisms of Action

Menthol has many different peripheral proposed mechanisms of actions. One such mechanism is the blocking of TRPA1, a thermoTRP which senses noxious cold. This inhibition of TRPA1 has been suggested by Klein et al. (2010, p.184). Macpherson et al. (2006) supported this by demonstrating, in rats, that menthol inhibits TRPA1 (p.336). This finding led Macpherson et al. to hypothesize that "menthol could act via inactivation of the pain-sensing thermoTRPs" in their study on the specificity of thermoTRP agonists (p.336). Pan et al. (2012) also supported this peripheral mechanism of thermoTRP inhibition in their investigation of the central mechanisms of menthol analgesia, though they noted that this mechanism is not fully respected (p.661). Pan et al. (2012) also proposed that menthol analgesia was based on the activation of TRPM8 (p.661). This was supported by Proudfoot et al. (2006), which tested TRPM8 analgesia by topically applying icilin on CCI rats. The inhibition of TRPA1 and activation of TRPM8 could prove to be a more effective treatment for the specific symptoms of thermal allodynia and hyperalgesia in diabetic neuropathy.
The ability to specifically activate TRPM8 leading to analgesia demonstrates its use for diabetic neuropathy, or any neuropathy in general if the patient cannot or chooses not to use capsaicin. However, at high doses, menthol can sensitize TRPM8 and cause pain, indicating a need for proper dosing and investigations into tolerance (Proudfoot et al. 2006, p.1599). This painful side effect should not occur, but it could, meaning menthol may not be appropriate for patients with extreme cold allodynia or hyperalgesia. It does appear that there is a huge difference in concentration that causes this pain, as Proudfoot et al. (2006) noted that "analgesic effects of icilin were seen at 200-fold-lower concentrations than those causing nonspecific sensory changes", with icilin being a far more potent TRPM8 agonist than menthol (p.1601). Therefore, an investigation should be done with more studies on humans or Phase 1 clinical trials. Rats cannot be used as they pose problems in the absorbance of menthol and vehicle, along with differences in hair, surface area, and penetration, as noted before. These types of studies would also help in proper dosing of menthol. Beyond TRPA1 and TRPM8, however, menthol also activates TRPV3, even at OTC concentrations (Macpherson et al. 2006, p.336). This may or may not have an effect on analgesia, but probably not through the pure activation of TRPV3.

Pan et al. (2012) finally proposed one last peripheral mechanism of action based on the inhibition of voltage-gated ion channels (p.661). Pan et al. (2012) suggested that menthol shifts the threshold of an action potential, blocks the action potential, or inactivates the fiber to inhibit voltage-gated ion channels (p.665). Menthol could cause analgesia by blocking voltage-gated sodium channels, blocking all nociceptive signals that travel up peripheral nerves (Pan et al. 2012, p.661). This voltage-gated inhibition is further supported by Brederson et al. (2006), which claimed "menthol was shown to inhibit voltage-gated sodium and calcium channels" (p.2). The inhibition of sodium and calcium channels could help diabetic neuropathy as the analgesia mediated by menthol may not be specific to a single type of pain, which could

help as diabetic neuropathy contributes to many different types of pain. Menthol also could be more effective in the treatment of a specific symptom of diabetic neuropathy, shooting pains, which could be caused by overactive sodium channels (Baron 2005, p.6).

Patel et al. (2007), however, provided another possible mechanism of action, stating that "similar to capsaicin, menthol may also cause analgesia by desensitizing nociceptive C fibres" (p.3). This mechanism of action for defunctionalization, the calcium overload of thermoTRP activation, by capsaicin may not occur with menthol. Indeed, Patel et al. (2007) claim that only capsaicin can accomplish defunctionalization, would make capsaicin a much better analgesic for diabetic neuropathy (p.492). Should menthol accomplish this as well, or have a more effective mechanism of action, it may be even better than capsaicin, as menthol appears to also have a central component to analgesia (Proudfoot et al. 2006, Pan et al. 2012). However, it is not known if menthol can compete with the ETC, meaning that menthol could be a far less effective peripheral analgesic than capsaicin. If menthol can also defunctionalize, Patel et al. (2006) claimed that menthol could defunctionalize TRPV1 afferents, which could make menthol more effective than capsaicin (p.392). Clinical studies or studies on humans are recommended to demonstrate these findings. Beyond the studies on effectiveness, studies on menthol's effects on the ETC should be done.

Central Mechanisms of Action

Menthol also has many different methods of central analgesia. In the introduction to their paper on menthol's analgesic effect on rats, Klein et al. (2010) stated that menthol activates κ-opioid receptors within the central nervous system, thereby producing analgesia (p.179). This was supported by Patel et al. (2007), who stated "menthol has been shown to selectively activate κ-opioid receptors", though they used this to explain menthol's anti-itch qualities in their paper "Menthol: A refreshing look at this ancient compound" (p.3). The activation of the κ-opioid pathway is indicative of a central mechanism of action for menthol analgesia. This, however, is contested by Proudfoot et al. (2006), who stated that icilin is opioid independent, as mu-opioid antagonist naloxone had no effect (p.1599). The discrepancy could be attributed to different pathways of activation, the difference being κ-opioid and mu-opioid. This central method of activation could be far more effective than capsaicin, which appears to only have peripheral activation. The activation of the opioid system could interfere with other analgesics, as other analgesics may activate the opioid system in other ways to provide analgesia. This investigation would have to be done through clinical trials and studies into drug interaction.

Klein et al. (2010) also proposed two different methods of analgesia: the activation of cold receptors by menthol that "centrally inhibit spinal nociceptive neurons" or the engagement of "suprasegmental or supraspinal circuits to result in descending inhibition of spinal nociceptive neurons" (p.184). One example of the first method was proposed by Pan et al. (2012) in "Central Mechanisms of Menthol-Induced Analgesia." Pan et al. (2012) proposed that menthol provides analgesia by "blocking Na+ and Ca2+ channels in dorsal horn neurons, an effect that has also been demonstrated in peripheral neurons (Swandulla et al., 1987; Gaudioso et al., 2012)" (p.671). This theory was mirrored by Brederson et al. (2013). The inhibition of Na+ and Ca2+ in the CNS would block the transmission of any nociceptive signal up the spinal cord. This stops pain from being felt at all, leading to higher qualities of life for diabetic neuropathic patients. Because it is so broad, this block of nociceptive signals could be used with great effect with any symptom of neuropathy.

This is much better than the pure peripheral analgesia of capsaicin, as many symptoms of diabetic neuropathy can be traced to central sensitization. Mechanical allodynia is one example of this type of symptom, characterized by pain from touch or light movement. One

proposed etiology for mechanical allodynia is the sensitization of the central nervous system is caused by sensitive C fibers, which release glutamate and substance P to sensitize dorsal horn neurons, which, in turn, sensitizes second-order dorsal horn neurons by upregulating sodium channels. Whereas capsaicin desensitizes the entire peripheral fiber, menthol may act on both peripheral and central neurons, inactivating sodium channels (Pan et al. 2012). If this is true, menthol may prove to be more effective than capsaicin in specifically treating mechanical allodynia. However, more investigation is needed, either in rats or, preferably, in humans through a clinical trial.

One example of the other type of central analgesia, the activation of a supraspinal circuit, could be the activation of GABA¬A. Pan et al. (2012) noted that when nerves were treated with bicuculline, a GABAA¬ antagonist, the strength of menthol induced currents were reduced, indicating that menthol induced currents are mediated by GABAA (p.665). However, Pan et al. (2012) realized that an effective dose of menthol would not be high enough to activate GABAA¬¬, leading to other hypotheses to be formulated, most likely, the blockage of sodium channels in dorsal root neurons (p.665). Due to this realization, it can the activation of GABAA is an unlikely central mechanism of action for analgesia. At the high doses necessary for the activation of GABAA¬, menthol causes nonspecific sensory changes and pain by sensitizing TRPM8 as noted before (Proudfoot et al. 2006, p.1599). This pain is another reason the activation of GABAA is not a central mechanism of action for menthol.

Another possible supraspinal circuit leading to menthol analgesia could be the activation of inhibitory Group II/III mGluRs, proposed by Proudfoot et al. (2006). Proudfoot et al. (2006) noted that "at the doses used, mGluR Group II/III antagonists selectively reversed icilin and menthol analgesia in sensitized responses, without any effects alone" (p.1602). Group II/III mGluRs are glutamate receptors which inhibit nociceptive signals from primary afferents (Proudfoot et al. 2006, p.1602). This marks a central mechanism without opioid response, which is a useful difference than many other analgesics with central mechanisms used with neuropathy. The lack of opioid response could also be effective for patients who have built a resistance to opioid analgesics, making treatment of diabetic neuropathy, and any pain in general, safer without increasing dosage of opiates. Lack of opioid response could also allow doctors to use opiates in coordination with menthol to more effectively treat all symptoms of pain. The combination of peripheral mechanisms of menthol and central mechanisms of menthol and opiates safely could effectively treat any symptom of diabetic neuropathy, from shooting pains in the PNS to mechanical hyperalgesia in the CNS. The interaction between these drugs, and drugs more commonly proscribed to treat long term diabetic neuropathy, has yet to be investigated in any clinical trials. Phase 1 clinical trials or general trials with humans on these drug to drug interactions is advised for the safety of any treatment of diabetic neuropathy with menthol and the safety of OTC use of menthol. Additionally, as stated previously, the addition of a central mechanism could make it more effective than topical capsaicin, which may be based solely in the peripheral nervous system. Yet, again, the effectiveness of capsaicin and menthol needs to be compared with a large scale trial on humans.

Additional Benefits of Menthol Use

Menthol could also have other benefits contributing to its prospective use in diabetic neuropathy. As stated previously, one major disadvantage with capsaicin use is the contamination of the environment, which can irritate the respiratory tract and burn skin (Anand and Bley 2011, p.491). Menthol cream could also contaminate the environment, however its effects would be less damaging and irritating than capsaicin, causing only a cooling sensation due to the activation of TRPM8. Therefore, menthol cream may be a better alternative for diabetic

peripheral neuropathic patients as poor patient compliance due to irritation by contaminated clothing would be reduced. Capsaicin also irritates the olfactory bulb by activating TRPV1 (Szallasi et al. 2006, p.546). For capsaicin cream, this irritation means that capsaicin can burn the nose and smell acrid. This can cause low patient compliance. Menthol, however, has a more appealing scent, leading to higher patient compliance.

Interestingly, a possible advantage to menthol use is alleviation of heat allodynia and heat hyperalgesia. Heat allodynia and heat hyperalgesia in diabetic neuropathy could be caused by the upregulation of TRPV1 on A fibers (Szallasi et al. 2006, p.549). Szallasi et al. (2006) conducted a review of research, investigating TRPV1's possibility as a new target for analgesics. The proposed mechanism for heat allodynia and heat hyperalgesia was supported by Baron's (2005) observations with peripheral nerve legions (p.550). Baron noted (2005) that peripheral nerve legions cause the upregulation of TRPV1 on A and undamaged C fibers in his analysis of scholarly work relating to the mechanisms of peripheral neuropathy (p.550). The proposition of upregulation on C fibers indicates a disparity between authors, though this could be explained by comparison of damaged fibers and undamaged fibers. The desensitization of both A fibers and C fibers by TRPV1 and TRPM8 analgesia could relieves this heat pain, however capsaicin can only affect these signals peripherally. The proposed central mechanisms of menthol analgesia could be more effective in treating this type of pain, as menthol could block sensation in the peripheral nerves and the spinal cord. This has yet to be investigated with any significant study, however.

A disadvantage to the use of capsaicin to treat diabetic neuropathy, as noted by Facer et al. (2007), is the decrease of TRPV1 in diabetic skin (p.10). This decrease may mean that menthol could be more effective in smaller doses than capsaicin in the same doses. The lowered dosage could negate any possible drug interaction. Another added benefit of this lowered dosage is decreased piquancy and pain from topical application. However, since TRPM8 nerves are lower in the dermis, a deeper penetrating vehicle must be used, such as tween or ethanol, which may increase costs and dosage for the drug, though the possible increased efficacy could offset that (Facer et al. 2007, p.7). Menthol appears to readily penetrate the skin, as in the use of mint oil as analgesic, meaning this may be a nonissue.

Another, more theoretical, side effect of capsaicin therapy is the degeneration of subcutaneous nerves, as, due to capsaicin's inhibition of the ETC, the cell may not be able to maintain the plasma membrane needed for cell communication and structure (Anand and Bley 2011, p.494). This can be measured immunohistochemical assays to PGP 9.5 or substance P, nerve protein markers specific to nociceptive neurons (Anand and Bley 2011, p.494). This could explain the substance P deletion noted by the Capsaicin Study Group (1991) in their clinical trial of capsaicin on diabetic neuropathy (p.4). These nerve markers could also be used to measure possible defunctionalization for menthol. It must be noted that both do not occur in the same time-scales, degradation of nerves taking significantly longer with repeated applications (Anand and Bley 2011, p.494). The length and applications would occur in diabetic neuropathy, as it is a constant issue. If defunctionalization occurs with menthol, the degradation of nerves could be a concern, though this has not been seen yet in capsaicin patients (Anand and Bley 2011, p.498). This degradation of nerves is important as it decreases enervation and sensation from cutaneous nerves. It also would cripple the sensation of pain, an important signal for the human body to carry. The loss of feeling and pain would make lives more dangerous, as people would not notice if they had injuries, big or small, in their skin. If defunctionalization does not occur, menthol could be considered safer, as it does not carry such a drastic theoretical side effect, no matter how rare.

Menthol is regularly an additive in toothpastes and foods, providing cool sensation

and minty taste. This, along with its widespread use in foods, cosmetics, and various other industries, along with its historical use as analgesic and herb in food, demonstrates its safety for human use. As noted before, however, drug to drug interactions have yet to be investigated in any significant study, and must be done before prescription of menthol for diabetic neuropathy. Menthol could also be cheaper than capsaicin. In a study done by Padmathilake, Wickramaarachchi, Anver, and Bandara in 2007, mint (mentha sylvestris) was grown hydroponically in a greenhouse. This study demonstrated menthol grown hydroponically can produce much more mint oil than menthol grown regularly (Padmathilake et al. 2007, p.198). The increased mint oil contains much of the menthol content for the plant, allowing for more menthol, and, therefore, more drugs, from a single plant. Padmathilake et al. (2007) also demonstrated that, despite the higher initial cost for hydroponic systems, the higher menthol content along with the efficacy and reusability of the system would make it more cost effective than regular mint or peppers (p.199). Another benefit of this hydroponic system is the loss of dirt, which loses nutrients over time, and the uselessness of manure, which increases cost. The higher menthol content of hydroponically grown mint would also reduce the cost of the drug. This reduced cost could make the far more profitable than capsaicin, which is produced by peppers that require soil and more water, causing potentially higher costs. The reduced cost could also make the drug cheaper while still maintaining profit margins. This decreased price would make the treatment of diabetic neuropathy easier on poor people with diabetes, if the treatment was as or more effective than capsaicin.

Beyond the previously mentioned cold nociception, menthol doesn't appear to have many side effects. However, Topp, Ledford, and Jacks (2013) noted that menthol can decrease arterial blood flow (p.220). This would mean that menthol should not be proscribed to any patient with vascular or circulation problems in their peripheral body, as menthol would decrease circulation. The loss of this circulation could cause irreparable damage to tissues. There may be even more side effects, but these cannot be seen without a large scale trial on humans. Clinical trials or large studies on humans would give a much larger bulk of data to find any potential side effect, while giving us more data on how useful it is in humans.

Menthol could also have use in different diseases. Colvin, Johnson, Mitchell, Fleetwood-Walker, and Fallon (2008) reported about the use of menthol to treat bortezomib-induced neuropathy, a symptom of chemotherapy (p.4519). This treatment, which involved the application of 0.5% topical menthol to skin and lumbar regions corresponding to pain, was highly effective, "demonstrat[ing] a rapid and significant therapeutic response using topical menthol to counteract bortezomib-induced neuropathic pain" (Colvin et al. 2008, p.4520). This was supported by Storey, Colvin, Mackean, Mitchell, and Fleetwood-Walker (2010) with a case of "carboplatin-induced peripheral neuropathy in a 71-year-old woman with a four and a half year history of Stage 4 epithelial ovarian cancer" (p.e3). The treatment and the result were similarly striking to the last case, but allowed the patient to continue treatment of chemotherapy (p.e3). These studies demonstrate the usage and effectiveness of menthol in treating chemotherapy induced peripheral neuropathy. This pain relief would help any chemo patient continue treatment with minimal pain. However, before any use of menthol, large scale trials should be done on humans. The reasons have been stated repeatedly before. Beyond cancer treatment and any peripheral neuropathy, menthol could be used to treat any type of pain topically, due to menthol's analgesic effect in both the PNS and the CNS. The multiple diseases that could be treated by menthol would mean that the large scale studies on humans would also be of use in the treatment of any other type of pain. Generally, the confirmation and expansion of the knowledge of menthol analgesia would allow for more varied treatment options for pain management, an invaluable resource in decreasing resistances to various drugs, and for the un-

derstanding of pain.

Conclusion

In summary, diabetic neuropathy is a painful symptom that decreases the quality of life for many diabetic patients. One of the most common treatments for diabetic neuropathy is capsaicin cream, which defunctionalizes nerves by causing the cell to swell with calcium and to lose the ability to produce energy. However, menthol can be a more viable alternative, as menthol has less potential side effects and could be more effective than capsaicin, due to the supposed existence of a central mechanism of action. These claims must be tested with a large scale human study or a Phase 1 clinical trial, which would demonstrate the validity and effectiveness of menthol in general. The trials or studies would also help with proper dosing, determination of vehicle, if needed, and safety with drug to drug interactions. These trials or studies would also allow for the use of menthol as analgesic for other neuropathies and pain conditions, such as chemotherapy induced peripheral neuropathy. Finally, these trials or studies would help expand the understanding of pain by providing more information on the mechanisms of action for menthol analgesia, leading to better analgesics and higher qualities of life for any patient with pain.

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