Cannabis-Based Medicines as a Novel Approach to Treating Wound-Related Pain

Are cannabis-based treatments effective for pain in wound care patients? These authors explore the research, scientific basis, advantages, as well as routes of administration, of cannabis-based medicines in providing pain relief and enhanced wound healing.

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Wound-related pain represents a domain of health care with an unmet need and a serious challenge for health care professionals who treat patients with integumentary wounds, involving both cutaneous membranes and mucous membranes. A remarkable two-thirds of patients with wounds experience wound-related pain.[1]

Wound-related pain is the result of primary factors such as tissue necrosis, ischemia, inflammation, edema, and infection; secondary factors also include peripheral and secondary neural sensitization, and peri-wound tissue pathology.[2–6] Wound-related pain also perpetuates the existence of the wound by inhibiting its healing via vasoconstriction and catabolic effects.[7,8] Malignant wounds and wounds with vasculopathic or autoimmune etiologies are the wound classes associated with the most suffering amongst patients.[1,9]

The International Association for the Study of Pain (IASP) stratifies wound-related pain into two categories: baseline pain and breakthrough pain, as reported by patients.[10–12] Baseline pain is constant and continuous pain.[10–12] In comparison, breakthrough pain is characterized as transitory episodes of intensified pain with rapid onset, whose existence is independent of baseline pain.[10–12] Breakthrough pain may be stratified further into the subclasses spontaneous pain and incident pain. Spontaneous pain occurs without a provocative trigger, whereas incident pain involves volitional triggers (specific and voluntary actions such as wound cleansing, dressing, or debridement) and non-volitional triggers (involuntary actions such as coughing, sneezing, or spasms).[10–12]

Breakthrough pain currently seems to be the more important focus of wound-related pain. Patients who experience breakthrough pain also experience higher levels of baseline pain, more intense peak pain, increased incidence of depression and anxiety, and decreased functionality.[2,13] These patients utilize more health care resources due to these exacerbated symptoms and thus have increased financial costs as well.[2] Fur-

thermore, only 25% of patients who experience breakthrough pain are satisfied with their pain treatment.[2,14]

Oral opioids and adjuvant analgesics such as non-steroidal anti-inflammatory drugs (NSAIDs), tricyclic antidepressants (TCA), and gabapentinoids are the major agents of the current paradigm.[11] Topical opioids, like methadone and morphine sulfate, as well as other topical analgesics, such as lidocaine and benzocaine, are lesser utilized agents, but still worth mentioning.[10,11]

Although this combination of traditional analgesics does relieve baseline pain to some degree, there are a plethora of adversities diminishing their ability to effectively treat breakthrough pain and wound-related pain as a whole. For example, their onset of action ranges from 30–90 minutes, making them ineffective for treating breakthrough pain.[15] In fact, TCA and gabapentinoids begin to show antinociceptive effects only after days or even weeks. Some routes of administration demonstrate rapid onset, like intravenous opioids, but are invasive, require hospital resources, and are not self-titratable. Oral and nasal transmucosal fentanyl is also efficacious in treating cancer-related breakthrough pain but carries risks for the patient and society in that fentanyl metabolizes through cytochrome P450 3A4 and is prone to drug diversion and accidental overdose.

Moreover, the status quo analgesics are fraught with adverse side effects including, but not limited to, respiratory suppression, delirium, renal failure, gastrointestinal hemorrhage, and methemoglobinemia syndrome in the case of benzocaine and lidocaine.[17] Opioids and NSAIDs are the most commonly employed analgesics.[18,19] They are also the leading cause of iatrogenic deaths.[20] With more than 70% of patients experiencing wound-related pain using opioids, it is logical to assume this overuse is contributing to the global opioid crisis.[18]

It is evident that the current methods for managing wound-related pain are inadequate and more detrimental than beneficial. It behooves clinicians to develop and investigate novel approaches to provide hope to the many patients suffering from wound-related pain.

FIGURE 1. It is evident that the current methods for managing wound-related pain are inadequate and more detrimental than successful. It behooves clinicians to develop and investigate novel approaches to provide hope to the many patients suffering from wound-related pain.

HOW CANNABIS-BASED MEDICINES WORK

The utilization of cannabinoids in conjunction with the other chemical classes found in the cannabis plant, namely the terpenoids and flavonoids, has increased over the past two decades.[13] The utilization of cannabis, however, dates back to antiquity when crude extracts were used by ancient Egyptian and Greek cultures for treating a variety of ailments.[20] Current and ongoing research suggests that cannabis-based medicines are a potential and promising candidate as a novel approach for treating wound-related pain.[20] These discoveries have been made possible by the global shift toward the legalization of medical cannabis and the elucidation of the endocannabinoid system.[20]

The endocannabinoid system is a chemical signaling system that has endured more than 500 million years of evolution and is present in every human organ system, especially the cutaneous and mucous membranes of the integumentary system.[13,21–23] It has been shown that the endocannabinoid system binds endogenous cannabinoids and an abundance of preclinical and clinical evidence demonstrates that activation of the endocannabinoid system via cannabinoid agonists induces analgesia.[24]

Interpreting the information that the endocannabinoid system is evolutionarily important, ubiquitous, exceedingly present in the largest organ system, and receptive to endogenous cannabinoids, one can logically deduce that cannabis-based medicine has the potential to treat integumentary conditions, notably wound-related pain.[21,22] In fact, studies have found that dysregulation of the endocannabinoid system results in integumentary wound pathophysiology, which includes wound-related pain.[13,21,22] Therefore, modulating the endocannabinoid system with the use of cannabis-based medicine may be a potential method for successfully and safely treating wound-related pain.

The cannabinoids, terpenoids, and flavonoids are the major chemical classes found in the cannabis plant.[25] Delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) of the canna-

FIGURE 2. The cannabinoids, terpenoids, and flavonoids are the major chemical classes found in the cannabis plant. Delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) of the cannabinoid family are the most popular and most studied agents found in the cannabis plant. The intrinsic anti-inflammatory and analgesic properties of all three classes are well established in the literature.

binoid family are the most popular and most studied agents found in the cannabis plant.[25] The intrinsic anti-inflammatory and analgesic properties of all three classes are well established in the literature.[25–28] There is also a theorized cumulative effect that these classes exhibit when they are used in combination known as the "entourage effect."[25]

Cannabis-based medicine combines these agents and various routes of administration in order to harness the synergistic effect to achieve robust analgesia. The preclinical and clinical research investigating the efficacy of cannabis-based medicine and its individual components as analgesic agents is a burgeoning area of study.[13,25,29] For instance, a 2017 case study documented rapid onset of pain relief in a patient with a malignant oral-buccal wound after implementing topical THC and CBD oils with vaporized cannabis flower.[30] Another study involving 3 cases of pyoderma gangrenosum implemented topical THC and CBD oil and reported not only rapid pain relief, but opioid-sparing effects after using the cannabis-based medicine.[31] A 2020 clinical trial employed topical proprietary cannabis-based medicine containing congeners of all three chemical classes to a cohort of patients with non-uremic calciphylaxis wounds.[32] Complete wound closure was observed in a mean of 2.5 months and zero utilization of all anaglesics was possible at a mean of 2.1 months.[32] In a cohort of pediatrics patients with epidermolysis bullosa, rapid pain relief, opioid sparing, and wound healing was observed.[33]

HOW TO ADMINISTER CANNABIS-BASED MEDICINES

Cannabis-based medicine is capable of improving healthcare outcomes for patients suffering from wound-related pain, while simultaneously reducing the use of the current status quo analgesics that cause adverse side effects and inhibit wound healing.[34,35] The authors propose the use of cannabis-based medicine as an independent therapy, and as an adjuvant therapy in some cases.[36]

Baseline pain can be treated with the use of oral/edible forms of cannabis-based medicine combined with low dose opioids since their onset of analgesia is around 30–60 minutes and their effects can last 8–12 hours.[37] In the case of breakthrough pain, a solution that is self-titratable with rapid onset is most appropriate. Accordingly, topical and vaporized cannabis-based medicines should be employed since their onset of analgesic activity is in the range of 5–15 minutes; their analgesic effects may last between 2–4 hours.[25,30,31,37]

Smoking and vaping are not ideal routes of administration due to the inhalation of toxic chemicals. However, the Volcano™ Medic 2 (Vapormed) is an approved vaporizer by Health Canada and may safely be used to vaporize the cannabis flower.

Topical cannabis-based medicine should be applied directly to the wound bed and as mentioned before, to the peri-wound tissues, since its pathophysiology influences wound-related pain.[4–6] The wound bed is lipophilic and thus the lipophilic topical cannabis-based medicine diffuses readily, unlike the peri-wound tissues, which are still intact and relatively hydrophilic.[30,31] This is an important consideration when developing topical cannabis-based medicine; having a topical analgesic for both wound bed and peri-wound tissues appears to be ideal.

Oral/nasal cannabis-based medicine sprays can also be utilized for treating breathrough pain but they are still undergoing development and less is known about their pharmacokinetics. The cannabinoids, terpenoids, and flavonoids are practically devoid of any serious side effects. THC, however, may induce psychotomimetic effects when delivered in higher dosages; this is a particularly frequent occurrence with those who have psychiatric illness or are cannabis naïve.[25,37] THC may also influence blood pressure by lowering it; this particularly concerns individuals with cardiac issues.[25,37] Medical cannabis, however, contains safer levels of THC for these reasons.[20]

CONCLUSION

The inadequacies and shortcomings of the current paradigm for wound-related pain management warrants the need for alternative strategies and

novel approaches. Cannabis-based medicine extends the possibility for improved pain relief, safer methods with less harm and fewer iatrogenic risks, self-titration and the reinstatement of personal agency, and enhanced wound healing.

We postulate that the use of cannabis-based medicine in a creative manner (i.e. multiple routes of administration and in combination with reduced dosages of status quo adjuvant analgesics) can improve overall relief of wound-related pain, improved quality of life, and reduce burdens and harm to patient and society. Further research into cannabis-based medicine is necessary to evaluate optimal dosages, protocols, and applications. ■

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