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BIOMEDICAL HYPOTHESIS

"Less pain with more gain"—Managing wound-related pain with cannabis-based medicines

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Abstract

Wound-related pain poses a serious challenge for patients and physicians. It is a complex pathophysiologic construct that may be stratified, from the patient's perspective, into baseline pain and breakthrough pain. The current paradigm for treating wound related pain involves the overuse of opioids and other co-analgesics with little regard for breakthrough pain. These standard medications have a propensity for deleterious side effects while some of them inhibit wound healing, effectively perpetuating the wound and the related pain. In particular, the overuse of opioids is a contributor to the global opioid crisis. It is evident that a new paradigm needs to be considered. Cannabis-based medicines are a prominent prospect under investigation for their potential to reduce dosages of status quo analgesics while effectively reducing pain. The authors propose a new paradigm that emphasizes the use of Cannabis-Based Medicines, delivered through multiple routes, while recommending the need for more foundational scientific investigation into mechanisms, and clinical controlled trials to determine optimal combinations, dosages, and protocols.

Integumentary wounds, involving both cutaneous membranes and mucous membranes, represent a significant and worrisome domain of unmet need within global healthcare. Wound-related pain is one of the most significant sources of suffering for patients, while representing one of the biggest challenges for wound clinicians. It is estimated that up to two thirds of patients with wounds experience wound-related pain.[1] The wound classes associated with the highest burden of wound-related pain include malignant wounds, and those associated with vasculopathic etiologies (arterial insufficiency, sickle cell disease, calciphylaxis, etc.), and autoimmune etiologies (pyoderma gangrenosum, rheumatoid arthritis, polyarteritis nodosa, etc.).[1,2] Wound-related pain is caused by primary factors such as tissue necrosis, ischemia, inflammation, edema, and infection, as well as secondary mechanisms such as peripheral and secondary neural sensitization.[3,4]

In accordance with the definitions supported by the International Association for the Study of Pain (IASP), patients with integumentary wounds report both baseline pain (BP) and breakthrough pain (BTP).[5-7] BP is described by patients as constant and continuous.[5-7] In contrast, BTP, defined as transitory intense exacerbations of pain of rapid onset, may be stratified into spontaneous pain and incident pain.[5-7] While spontaneous pain occurs without any provoking events, incident pain may be volitional (associated with a specific voluntary trigger or procedure, such as wound cleansing, dressing changes, or debridement), or nonvolitional (initiated by involuntary triggers, such as spasms, coughing, or sneezing).[5-7] The fact that BTP may be more of a problem than BP is reflected by research that reports only 25% of patients who experience BTP are satisfied with their overall degree of pain management.[3,8] Patients experiencing BTP also report higher overall pain scores as well as being associated with higher utilization of medical and hospital resources and thus increased financial costs.[3] Underrecognized is the fact that wound-related pain may inhibit

Abbreviations: 5-HT, 5-Hydroxytryptamine receptor; A_{2A}, adenosine 2A receptor; CB_1, cannabinoid receptor 1; CB_2, cannabinoid receptor 2; CBD, cannabidiol; CBM, cannabis-based medicines; ECS, endocannabinoid system; GlyR, glycine receptor; GPR, G protein-coupled receptor; NF-κB, nuclear factor kappa light chain enhancer receptor; PPAR, peroxisome proliferator-activated receptor; TCBM, topical cannabis-based medicines; THC, delta-9-tetrahydrocannabinol; TRPA, transient receptor potential cation channel subfamily A; TRPM, transient receptor potential cation channel subfamily M; TRPV, transient receptor potential cation channel subfamily V; α_2R, alpha-1 adrenergic receptor.

wound healing through a number of direct and indirect mechanisms, namely vasoconstriction and catabolic effects, respectively.[9,10] Needless to say, wound-related pain also leads to reduced quality of life, reduced functionality, and emotional symptoms, such as anxiety and depression.[11]

The current standard of care for wound-related pain largely involves the use of oral opioids and adjuvant analgesics such as Non-Steroidal Anti-Inflammatory Agents (NSAID), Tri-Cyclic Anti-Depressants (TCA), and Gabapentinoids (GPT).[6] Some wound clinicians also employ topical opioids, such as morphine sulfate and methadone, as well as topical benzocaine and lidocaine.[5,6] Although this collection of agents may have some variable effect on BP, at best, their onset of action ranges between 30 and 90 minutes, thus precluding effective analgesia for BTP.[12] Furthermore, TCA and GPT usually require days and weeks to begin to show even marginal analgesic responses. Intravenous opioids exhibit analgesia within 5 to 10 minutes of administration, but this route is invasive, associated with higher opioid-related risks and side effects, and is only suitable for hospital inpatients, while being neither easily self-administered nor self-titratable. Although oral and nasal transmucosal fentanyl has demonstrated efficacy in the treatment in the management of cancer BTP,[13] it carries significant risks for both patient and society owing to its metabolism through cytochrome P450 3A4, and its propensity for drug diversion and accidental overdose. Overall, the current melange of opioids and adjuvant analgesics have a plethora of serious potential adverse side effects that include respiratory suppression, delirium, renal failure, gastrointestinal hemorrhage, and in the case of benzocaine and lidocaine,[14] the life threatening methemoglobinemia syndrome. Moreover, opioids[15] and NSAID[16] agents have both been found to directly inhibit wound healing while being the top causes of iatrogenic deaths among pharmaceutical agents. More than 70% of patients suffering from wound-related pain use opioids[15] and this is a likely contributor to the global opioid crisis.[11] Therefore, it is clear that this current standard of care is inadequate, and it behooves wound clinicians to seek out novel approaches to provide their patients with an improved level of hope.

Over the past two decades, a renaissance in health care has been evolving with the increased utilization of cannabinoids together with other molecular classes expressed in the cannabis plant.[11] Medicines derived from the cannabis plant have been used since antiquity by numerous ancient cultures for a range of healthcare concerns, such as pain, anxiety, spasms, and so on.[11] Furthermore, ancient cultures in both Egypt and Greece employed crude extracts from the cannabis plant, compounded within lipophilic media, such as animal fat, butter, and oils, to treat a variety of integumentary wounds, both traumatic and disease related. Research into cannabis-based medicines (CBM) has been made possible by the progressive global trend of legalizing medical cannabis. The discovery of an endogenous chemical signaling system that operates through a series of receptors that bind endogenous "cannabinoid-like" agonists that are congeners of many of the chemical classes found in the cannabis plant validates the therapeutic potential of CBM. Dubbed the endocannabinoid system (ECS), it is one of only two chemical signaling systems that has survived in the phylogeny of vertebrates for more than 500 million years.[11] The ECS is expressed in all organ systems of the human body, and prevalent in all components of the integumentary system, cutaneous and mucous membranes alike.[17,18] Given that the integumentary system is the largest and heaviest organ system in the human body, it seems logical to project that CBM holds much promise for the treatment of integumentary conditions in terms of relieving WRP and potentially promoting the healing of wounds.[17,18] It has been theorized that dysregulation of the ECS contributes significantly to the pathophysiology of integumentary wounds, which includes wound-related pain.[11,17,18] ECS receptors are varied and include the classic extracellular CB1 and CB2 receptors together with other extracellular receptors involved in pain pathways, such as the TRPV, TRPA, TRPM, GPR, GlyR, A_{2A}, α_2R, and 5-HT families of receptors.[17,18] Although not yet fully elucidated, there is evolving preclinical and human evidence showing that complex interactions between cannabinoid and non-cannabinoid molecules with multiple receptor families promotes analgesia.[19] However, data on optimal therapeutic combinations and dosages remains under investigation. Beyond their extensive extracellular presence, the ECS is also involved intracellularly through the PPAR family of nuclear receptors and the NF-κB pathway.[20,21] The fact that ECS receptors are present intracellularly, upon the various cellular organelles, may allow for epigenetic modulation to promote both analgesia and wound healing.[20,21]

CBM contain active agents derived from the cannabis plant.[11] The most plentiful and clinically active compounds belong to the cannabinoid, terpene, and flavonoid chemical classes.[22] Among the more than 70 different cannabinoids yielded from the cannabis plant, the most studied are delta-9-Tetrahydrocannabinol (THC), and Cannabidiol (CBD).[22] All of the three main chemical classes are widely recognized for their intrinsic anti-inflammatory and analgesic properties.[22] Moreover, it is theorized that they operate in a synergistic manner to potentiate these effects in a phenomenon termed the "entourage effect."[22] There is a growing body of both preclinical and human research that is demonstrating the efficacy of the various components of CBM for analgesia, when administered through a number of routes.[11,22,23] A case report from 2017, using vaporized cannabis together with topical cannabis oils containing both THC and CBD, reported rapid onset of pain relief in one patient with malignant oral-buccal wounds.[24] Additionally, three cases of pyoderma gangrenosum experienced rapid pain relief together with opioid sparing while using topical cannabis oil containing both THC and CBD.[25] A cohort of patients with nonuremic calciphylaxis leg wounds, from a clinical trial using a topically applied proprietary CBM containing cannabinoids, terpenes, and flavonoids, demonstrated complete wound closure within 2.5 months and zero utilization of all analgesics at 2.1 months.[26] A cohort of children with Epidermolysis Bullosa experienced relief of WRP, opioid sparing, and a degree of wound healing in an open label trial involving topical CBD.[27]

CBM has the potential to improve overall wound-related pain management, addressing both BP and BTP, while reducing the utilization of drugs, particularly opioids and NSAID, that are already deleterious through their direct inhibition of wound healing and associated

adverse side effects. Many studies, including a recent systematic review, corroborate this idea of using CBM as adjuvant therapies to reduce the utilization of status quo analgesics.[28,29] Therefore, the authors propose a new treatment paradigm for wound-related pain in Figure 1. The use of oral/edible forms of CBM, containing combinations of cannabinoids, such as THC and CBD, together with terpenes and flavonoids, along with lower dose opioids, have the potential to reduce BP while mitigating the risk of wound inhibition associated with high dose opioids and NSAID. CBM, in oral/edible formats (oils, caplets, baked goods, etc.), have demonstrated onset of analgesic activity within 30 to 60 minutes; this response may last 8 to 12 hours, thus necessitating administration 2 or 3 times daily. The need for preemptive, preventative, and prompt treatment of BTP may be achieved, in a noninvasive and patient self-titrated fashion, through the use of combinations of vaporized cannabis flower, topical CBM applied to both wound bed and peri-wound tissues, and rapid onset CBM sprays, currently under development, for administration buccally and intranasally. Smoking of dry cannabis flower is not recommended as it is associated with inhalation of the toxic products of complete combustion. However, vaporization of dry cannabis flower, using a Health Canada approved medical device such as the Volcano Medic 2 (License No. 103842), does not involve combustion and thus is safe for both users and bystanders. Vaporized dry cannabis flower has demonstrated onset of analgesic activity within 5 to 10 minutes; this response may last 2 to 4 hours.[22,30] Other forms of vaporization using devices that are not approved by regulatory bodies, such as "e-cigarette" technologies, are not recommended as they utilize mixtures that contain processed cannabis extracts together with oils, flavoring agents, and stabilizers; the use of such unregulated devices and their mixtures has been associated with the release of Vitamin E Acetate that has been linked with the development of Vaping-related lung illness.[31] Although pharmacokinetic data on topical CBM is sparse, case reports have noted onset of action within 5 to 15 minutes along with a duration of action lasting several hours.[24,25] Thus, topical CBM may be useful to treat both BP and BTP by virtue of their ease of application and being amenable to self-titration by the patient. Although Terpenes, Flavonoids, and CBD are relatively devoid of serious side effects, systemically administered THC may be associated with psychotomimetic side effects, particularly in patients with psychiatric illness, and those who are cannabis naïve.[22,30] THC may also lead to a slight lowering of blood pressure and thus should be used with caution in those patients with cardiac issues.[22,30] Therefore, THC dosages need to be skilfully individualized and titration needs to be carried out under medical supervision.

A new approach to managing wound-related pain emphasizing CBM, delivered through a number of routes, offers hope for improved pain relief, using noninvasive and safer methods that may be both

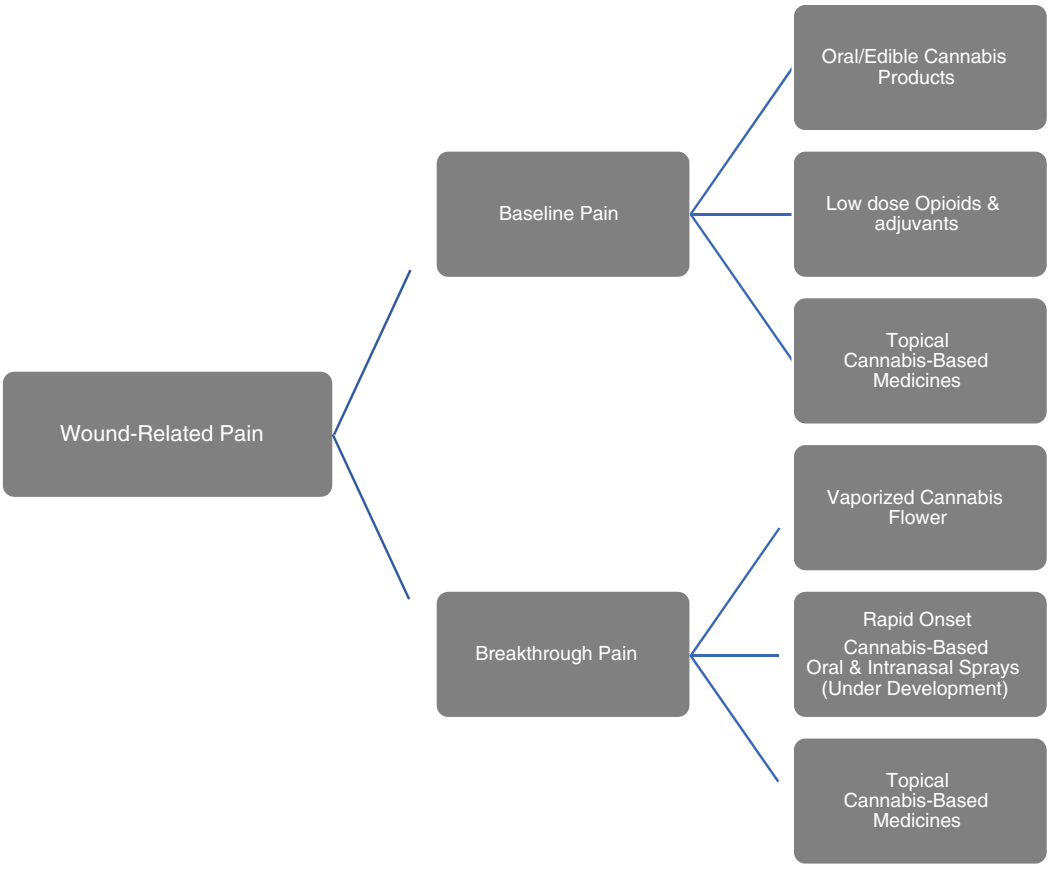

FIGURE 1 Proposed paradigm for treating wound-related pain emphasizing the use of cannabis-based medicines [Color figure can be viewed at wileyonlinelibrary.com]

self-administered and self-titrated, while reducing overall iatrogenic risks. Thus, the use of creative combinations of CBM, alongside minimized doses of opioids, may be regarded as an overall "harm reduction" strategy that may indeed lead to "less pain with more gain." Therefore, further basic scientific research into the role of the ECS in relation to integumentary diseases and wounds is warranted together with clinical controlled trials in patients with wound-related pain to determine optimal dosages, compositions, and protocols.

CONFLICT OF INTEREST

VM is the President and CEO of VinSan Therapeutics Inc which holds intellectual property and a patent portfolio for cannabis-based medicines for integumentary and wound management.

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