Research Findings Relating to Cannabidiol (CBD) and its Influence on Inflammation, Neuropathic Pain and Nociceptive Pain

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Disease or injury can impact the sensory nervous system, which can result in impaired transmission of sensory nerve impulses to the brain. When the sensory nervous system is compromised, it can lead to acute or chronic pain and in some cases a lack of sensation is experienced.

Neuropathic pain results from irritated, damaged, or dysfunctional nerves. This type of pain state holds many complexities as it is difficult to identify, diagnose and manage as often few objective signs are present. What makes the treatment of neuropathic pain especially complicated is that traditional pain medications are mostly ineffective. This has led many providers to prescribe unconventional medications, such as antidepressants, antiseizure medications, heart arrhythmia medications, transdermal lidocaine and in some cases narcotics to help those afflicted with neuropathic pain find relief. The effective management of neuropathic pain is dependent upon the underlying cause. Should the cause of the pain be reversible, the peripheral nerves have a chance of regenerating and the pain could possibly be resolved with time - in some cases, the resolution of nerve pain can take many months or years.

Researchers conducted a preclinical study to explore the mechanism through which CBD can impact neuropathic pain. They found that repeated treatment with CBD acts to reduce pain and "impaired [serotonin] 5-HT neurotransmission under neuropathic pain conditions" (De Gregoria et al., para. 1, 2018). Additionally, rodent models show that CBD has the potential to "significantly suppress chronic inflammatory and neuropathic pain without causing apparent analgesic tolerance" (Xiong et al., 2012, p. 1121). A study was conducted to explore the analgesic effect of cannabinoids in a rodent model of sciatic nerve pain. The rats were exposed to chronic constriction injury of the sciatic nerve. The researchers found that a moderate dose of 2.14 mg/kg "completely alleviated the thermal and mechanical hyperalgesia, and mechanical allodynia without side effects" (Herzberg,

Eliav, Bennett, Kopin, 1997, para. 1). In conclusion, the researchers identified cannabinoids as a promising option for the treatment of painful neuropathy.

When discussing pain, a distinction needs to be made between neuropathic pain and nociceptive pain. Nociceptors are the nerves that sense and respond to injury. Upon activation, the nociceptors transmit pain signals to the brain. Examples of nociceptive pain include bone fractures, sprains, burns, bruises and acute or chronic inflammation. This type of pain is usually localized, constant and can be accompanied by aching or throbbing. Visceral pain or organ pain is a subtype of this pain category and is often episodic and poorly localized. Nociceptive pain is usually time limited because once the damaged tissue heals, the pain will typically resolve. Additionally, nociceptive pain is more effectively managed with commonly available over-the-counter or prescription pain medications. However, traditional pain remedies are fraught with risks such as physical dependency, addiction, withdrawal symptoms, side effects and the potential for overdose.

Due to the inherent risks and potential for ineffective treatment of pain through conventional means, many people that suffer with acute or chronic pain are looking to find alternative treatment options. When reviewing the scientific literature, the use of CBD is showing much promise as a safe and effective alternative option for pain management. Cannabinoids have been found to block pain in every laboratory pain model study reviewed. In models of acute pain, cannabinoids have been shown to be “highly effective against thermal, mechanical, and chemical pain, and are comparable to opioids in potency and efficacy” (Lynch & Clark, 2003, p. 496). In chronic pain models, cannabinoids have been shown to control both inflammatory and neuropathic pain.

Over twenty percent of American adults live with arthritis – osteoarthritis or rheumatoid arthritis – and many are looking to cannabinoids to reduce their pain and inflammation without unwanted side-effects. A recent cross-sectional study used a questionnaire to assess the reasons for CBD use by self-described users. The researchers found that chronic pain and arthritis/joint pain were among the top three conditions reported by the study respondents (Carroon & Phillips, 2018). Those afflicted with arthritis are finding relief when applying CBD topically to painful joints. A study published in 2016 examined the efficacy of transdermal CBD in a rodent arthritic knee joint model. CBD gels with varying concentrations of CBD were applied for 4 days to the arthritis induction – low dose CBD gels of 0.6mg/day and 3.1mg/day and high dose CBD gels of 6.2mg/day and

62.3mg/day. Joint inflammation and pain were assessed 4 hours after gel application. The low dose CBD gels were found to produce no results across all tests. The 6.2mg/day CBD gel dose produced significant results in addressing both pain and inflammation. Increasing that dose by ten-fold to 62mg/day did not result in additional improvements. This finding is consistent with previous studies that show a bell-shaped-dose-dependency curve for CBD. The high dose CBD gels were found to significantly decrease the knee joint circumference increase that occurred following the insult from 30.9 $\pm$ 0.3% to 16.7 $\pm$ 2.8%. Histological study found that pro-inflammatory markers returned to baseline and synovial membrane thickening was reduced by more than 50% from 1788μm pre-treatment to 767μm post-treatment. The researchers concluded that topical CBD holds therapeutic potential to address arthritis pain and inflammation without side-effects (Hammell et al., 2016).

The question is, how does CBD exert its analgesic and anti-inflammatory effects on the mammalian body? The answer is through its direct interaction with the endocannabinoid system. This body system has been found to parallel and directly interact with other major pain control systems in the body, namely (1) endorphin/enkephalin, (2) vanilloid/transient receptor potential, and (3) inflammatory systems (Russo, 2008, p. 246). As a result, the endocannabinoid system is integral to the regulation of inflammation and pain. It is understood that inflammation contributes to both nociceptive and neuropathic pain. For this reason, CBD is proving instrumental as a therapeutic that can both block inflammation and decrease pain. Philpott, O'Brien and McDougall (2017) explain that from a pharmacological stand-point, "CBD has a complex signaling mechanism whereby it can both activate and silence" innate cannabinoid receptors (p. 2442). Research shows that "CBD-based analgesia is associated with potent immune-modulatory, anti-inflammatory, and antioxidant activity" (Carroon & Phillips, 2018, p. 156). Preclinical murine models show that CBD acts as an agonist for many cell-surface receptors that are associated with anti-inflammatory activity. It is through this action that CBD reduces inflammatory cytokines in rodent models of chronic and acute pain and many types of inflammatory disease (Carroon & Phillips, 2018). Researchers explain that CBD also acts to inhibit enzymes such as fatty acid amine hydrolase (FAAH) and monoacylglycerol lipase (MGL) that are known to degrade naturally occurring endocannabinoids in the body. The inhibition of these enzymes leads to "increased endocannabinoid levels, analgesia and opioid-sparing effects in preclinical models of pain" (Carroon & Phillips, 2018, p. 157). The opioid-sparing effect of cannabis

refers to the synergistic interaction that exists between cannabinoids and opioids. Research indicates that the endogenous endocannabinoid system is responsible for pain and inflammation modulation through the same brainstem circuitry responsible for opioid analgesia. The co-administration of a cannabinoid together with opioids may result in a lower opioid requirement (Lynch & Clark, 2003, p. 496). Evidence shows that the use of cannabinoids may aid with "opioid detoxification and weaning, thus making it a potential weapon in battling the opioid epidemic" (Baron, 2018, para. 3). Additionally, clinical studies indicate that through interaction with the serotonin (5-HT) 1A receptor, CBD treatment possesses analgesic effects (De Gregoria et al., 2018).

Plants from the *cannabis* genus "vary widely in the composition of cannabinoids, terpenes, flavonoids, and other compounds" (Baron, 2018, para. 1). These components all work together in a synergistic manner to provide various therapeutic benefits for the management of pain and inflammation. For thousands of years people have used cannabinoids for a wide range of conditions with great success. It is encouraging that after many years of prohibition, we can now study and utilize this amazing herb, which research shows to be so effective at addressing pain and inflammation without all of the risks that conventional remedies hold.

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