REVIEW ARTICLE

The Importance of Interplay between the Endocannabinoid System and Cannabidiol in Pain Relief

by Healthcare International Research Limited

PAIN IS AN EXTANT UNIVERSAL PROBLEM

Each year, the Global Pain Index provides a global, cross-sectional & representative assessment of the state of pain in the world. The report captures the perceived immediate impact of pain on individuals' everyday lives, their health, their feelings, emotions, motivations and behaviours from their experience at a global and country level[1]. The 110-page report provides sufficient evidence across multiple resources that pain escalation across the world is prevalent and increasing at an alarming rate. The salient metrics for the year 2020 are extrapolated and highlighted below:

- 93% of the global population suffered from pain;
- 34% of the global population are in pain every day;
- 20% of chronic pain persists in people under 30 years old;
- 72% of affected people believe pain decreases their quality of life;
- 77% of affected people wish they could control their pain better;
- 76% of affected people want to learn more about how to manage their pain;
- 65% cannot be happy when experiencing pain;
- 30% of pain sufferers visit a doctor for treatment and 23% of those that visit a doctor are dissatisfied with the treatment;
- 25% will use natural remedies to help with pain management;
- 6% of affected people take Cannabidiol based treatments.

The report provides overwhelming data that pain is an extant global problem that is spiralling out of control. Moreover, it highlights the urgent need for pain management therapies and treatments to be fully evaluated to eliminate or reduce the feeling of pain and reverse the increasing trend of pain related diseases. Sadly, most medical experts and academics conclude that despite colossal financial and economic costs, the real cost of pain is happiness[2]. With 76% of individuals suffering with pain wanting to learn more about how to manage their pain, this paper may increase awareness of the pain phenomenon and educate individuals about emerging and innovative treatments involving Cannabidiol.

CANNABIDIOL AND PAIN MANAGEMENT

Over the last twenty years, clinical evidence suggests that Cannabidiol (CBD) provides therapeutic benefits in certain conditions, and improves quality of life[3]. Importantly, CBD has gained significant attraction because it is devoid of the psychoactive effects associated with tetrahydrocannabinol (THC)[4]. The increase of empirical research into the impact and effects of CBD have increased the understanding of the mechanisms of cannabinoid-induced analgesia and provided therapeutical strategies for treating pain in humans. The mechanisms of the analgesic effect of cannabinoids include inhibition of the release of neurotransmitters and neuropeptides from presynaptic nerve endings, modulation of postsynaptic neuron excitability, activation of descending inhibitory pain pathways, and reduction of neural inflammation[5]. There is reliable evidence to support the use of CBD in the treatment of chronic pain based on scientific evidence. The National Academy of Sciences, Engineering and Medicine has evaluated more than 10,000 scientific abstracts and established that there is 'conclusive or substantial evidence' for the use of CBD in treating chronic pain in adults[6].

THE ENDOCANNABINOID SYSTEM IN PAIN MANAGEMENT

In the 1960s, scientists studying cannabis identified and isolated 2 compounds: delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). They called these compounds *cannabinoids* since they were derived from the cannabis plant. Further research in the 1990s, demonstrated the receptors CBD would attach to and revealed an entirely new molecular system existing within the human body. It was named the Endocannabinoid System (ECS) and is considered a master regulatory system[7]. Not only does it

1 Global Pain Index 4 Report (2021) *GSK Consumer Healthcare* available online at: https://www.gsk.com/media/6351/2020-global-plain-index-report.pdf

2 Bastian, B. (2018) *The other side of happiness: Embracing a more fearless approach to living*. Penguin UK.

3 Kalant, H. (2001) 'Medicinal Use of Cannabis: History and Current Status', *Pain Res. Manag.* 6 (2), 80–91.

4 Leweke, F. M., Piomelli, D. *et al.*, (2012). 'Cannabidiol Enhances Anandamide Signalling and Alleviates Psychotic Symptoms of Schizophrenia', *Transl. Psychiatry* 2, E94.

5 Vučković, Sonja et al., (2018) 'Cannabinoids and Pain: New Insights From Old Molecules', *Frontiers in pharmacology* vol. 9, 1259.

6 NASEM (2017) *National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board on Population Health and Public Health Practice; Committee on the Health Effects of Marijuana: An Evidence Review and Research Agenda. The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research*. Washington, DC: National Academies Press.

7 Pertwee, R. (2006) 'Cannabinoid pharmacology: the first 66 years', British Journal of Pharmacology, 147 (Suppl 1), 163-171.

have a powerful effect on other systems in the body, it is one of the body's most important tools for maintaining homeostasis and balance[8]. Dr Svensson, Dean Emeritus and Professor at the Department of Medicinal Chemistry and Molecular Pharmacology at Purdue University College of Pharmacy, succinctly states the ECS is present at essentially all levels of the anterolateral system, which is responsible for the perception and modulation of pain[9]. A seminal paper culminating research over a ten-year timeframe concludes that like other systems in the body, the ECS can be thrown out of balance due to trauma, stress, fatigue or inflammation. Clinical endocannabinoid deficiency can be associated with various conditions including pain, inflammatory and neurologic conditions[10]. The body's natural endocannabinoids function when needed; when the body senses inflammation or pain and needs to return to homeostasis it will release endocannabinoids that bind to cannabinoid receptors. Moreover, if the human body does not produce enough endocannabinoids then supplementation may be needed.

TOPICAL APPLICATION OF CBD TO OPTIMISE THE ECS

The topical application of CBD and the benefits it brings to restore and optimise an unbalanced and under-performing ECS has been researched sufficiently with most important studies concluding that application of CBD does contribute to a healthy ECS and attenuates inflammation and pain without adverse side-effects[11]. Some medical practitioners believe that topical application of CBD is favourable over ingestion for several reasons. Firstly, the risk of adverse reaction is increased during ingestion because potentially unregulated CBD products may be adulterated with potentially toxic compounds[12]. Secondly, when CBD is administered topically to effected areas of pain the speed of delivery may be quicker than ingesting CBD oil. Thirdly, high concentrates of CBD can be applied directly to affected areas of pain that can rapidly deliver the required levels of endocannabinoids to areas where it is needed; ingestion of CBD oil distributes the concentrate of CBD around the entire body that may result in painful areas not receiving the required levels. Finally, topical drug application avoids gastrointestinal administration, first pass metabolism, providing more constant plasma levels[13].

FUTURE PAIN MANAGEMENT

Pain is a devastating global disease that deprives people of their health & happiness. It continues to be an extant medical problem. Despite widespread evidence presented by medical practitioners, laboratories, scientists, academics and research participants into the healing properties of CBD for pain management, more research needs to be completed to validate claims. Unfortunately, efforts to discuss the dangers of CBD use have been severely lacking and require immediate attention to prevent the irreparable harm to the masses from the tsunami of CBD products[14]. That being said, a quick deep dive across the number of success stories of how the topical application of CBD has optimised the ECS to provide effective treatment for pain bolsters further the claim that CBD is a credible treatment for pain management.

This white paper was completed for HIR by Harry Rule. Harry is a leading independent researcher specialising in qualitative research across a wide range of sectors. He holds a Masters of Research and has recently completed a Doctor of Business Administration and leads HIR's research team.

8 Sallaberry C. & Astern L. 'The endocannabinoid system, our universal regulator', Journal of Young Investigators. June 2019; 34 (6): pp. 48-55.

9 Svensson, C.K. (2020) 'CBD for the treatment of pain: what is the evidence?', *Journal of the American Pharmacists Association,* Vol. 60, Issue 6, pp.80-83.

10 Russo E. B. (2016) 'Clinical Endocannabinoid Deficiency Reconsidered: Current Research Supports the Theory in Migraine, Fibromyalgia, Irritable Bowel, and Other Treatment-Resistant Syndromes', *Cannabis and cannabinoid research*, *1*(1). pp,154–165.

11 Ashton, L. (2020) Cbd and sports: How hemp oil improve athletic performance.

12 Argueta, D. A., Ventura, C. M., Kiven, *et al*., (2020) 'A Balanced Approach for Cannabidiol Use in Chronic Pain', *Frontiers in pharmacology*, *11*, p.561.

13 Hammell, D. C., Zhang, L. P., Ma, F. *et al*., (2016) 'Transdermal cannabidiol reduces inflammation and pain-related behaviours in a rat model of arthritis', *European Journal of Pain (London, England)*, *20*(6), pp. 936–948.

14 Argueta, D. A., Ventura, C. M., Kiven, *et al*., (2020) 'A Balanced Approach for Cannabidiol Use in Chronic Pain', *Frontiers in pharmacology*, *11*, p.561.