## CANNABINOIDS & PAIN

Pain is one of the most frequent health complaints. In the United States, "back pain" is the most common chief complaint at medical offices and emergency rooms. Cannabinoids have an important role in pain relief. It works in at least two ways to improve pain: by modulating inflammatory responses that cause pain and by reducing nociceptive thresholds in both the central nervous system and the periphery. In other words, cannabinoids work by stopping pain at its source and by decreasing the perception of pain. CBD primarily alters activity in CB2 receptors. CB2 receptors contribute to "antinociception by inhibiting the release of pro-inflammatory factors by non-neuronal cells located near nociceptive neuron terminals," specifically in inflammatory hyperalgesia and europathic pain, (Manzanares et al., 2006, p 240). Cannabinoids may indirectly influence NMDA receptor activity and control NMDA receptor over activation in neuropathic pain pathways (Sanchez-Blazquez et al., 2014). Additionally, CBD is a positive allosteric modulator at ∂1 and 1ß glycine receptors (Xiong et al., 2012).

The most research on cannabinoids has been in the areas of pain. Many studies have investigated pain as their primary outcome, but dozens of studies with other primary outcomes, such as HIV, cancer, spasticity, etc., have also evaluated pain as a secondary outcome. The results are overwhelmingly supportive that cannabinoids are affective analgesics.

**Sánchez-Blázquez, P., Rodríguez-Muñoz, M., & Garzón, J. (2014). The cannabinoid receptor 1 associates with NMDA receptors to produce glutamatergic hypofunction: implications in psychosis and schizophrenia. Frontiers in pharmacology, 4, 169.**

**Whiting, P. F., Wolff, R. F., Deshpande, S., Di Nisio, M., Duffy, S., Hernandez, A. V., ... & Schmidlkofer, S. (2015). Cannabinoids for medical use: a systematic review and meta-analysis. Jama,313(24), 2456-2473.**

**Xiong, W., Cui, T., Cheng, K., Yang, F., Chen, S. R., Willenbring, D., ... & Zhang, L. (2012). Cannabinoids suppress inflammatory and neuropathic pain by targeting 3 glycine receptors. Journal of Experimental Medicine, jem-20120242.**

Whiting et al.'s systematic review in JAMA included 28 clinical trials evaluating cannabinoids and pain. The authors concluded that there is moderate-quality evidence that cannabinoids may result in marked pain reduction, (Whiting et al., 2015).

A second systematic review on neuropathic pain included fifteen randomized controlled trials found that cannabinoids were more effective than placebos, but warned about possible minor adverse events, such as intoxication. Intoxication was due to higher levels of THC, which are not found in hemp products (Petzke et al., 2016).

Lastly, the National Academies of Science, Engineering and Medicine conducted an extensive systematic review aimed at evaluating cannabinoid therapies and safety (2017). They reached nearly 100 conclusions. One of them is that there is "extensive evidence" of cannabinoids' efficacy in pain relief. They also concluded that cannabinoids are well-tolerated. Finally, the study authors remarked that cannabinoid therapy or supplementation may play a role in reducing opioid intake.

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Manzanares, J., Julian, M. D., & Carrascosa, A. (2006). Role of the cannabinoid system in pain control and therapeutic implications for the management of acute and chronic pain episodes. Current neuropharmacology, 4(3), 239-257.

National Academies of Sciences, Engineering, and Medicine. (2017). The health effects of cannabis and cannabinoids: the current state of evidence and recommendations for research. National Academies Press.

Petzke, F., Enax-Krumova, E. K., & Häuser, W. (2016). Efficacy, tolerability and safety of cannabinoids for chronic neuropathic pain: A systematic review of randomized controlled studies. Schmerz (Berlin, Germany), 30(1), 62-88.

Sánchez-Blázquez, P., Rodríguez-Muñoz, M., & Garzón, J. (2014). The cannabinoid receptor 1 associates with NMDA receptors to produce glutamatergic hypofunction: implications in psychosis and schizophrenia. Frontiers in pharmacology, 4, 169.

Whiting, P. F., Wolff, R. F., Deshpande, S., Di Nisio, M., Duffy, S., Hernandez, A. V., ... & Schmidlkofer, S. (2015). Cannabinoids for medical use: a systematic review and meta-analysis. Jama,313(24), 2456-2473.
Xiong, W., Cui, T., Cheng, K., Yang, F., Chen, S. R., Willenbring, D., ... & Zhang, L. (2012).

Cannabinoids suppress inflammatory and neuropathic pain by targeting ∂3 glycine receptors. Journal of Experimental Medicine, jem-20120242.

## PLEASE SEE BELOW FOR ADDITIONAL REFERENCES OF PAIN-SPECIFIC REVIEWS, ALL OF WHICH CONFIRM CANNABINOIDS ROLE IN PAIN RELIEF:

Martín-Sánchez E, Furukawa TA, Taylor J, et al. Systematic review and meta-analysis of cannabis treatment for chronic pain. Pain Med. 2009;10:1353-68.

Deshpande A, Mailis-Gagnon A, Zoheiry N, et al. Efficacy and adverse effects of medical marijuana for chronic noncancer pain. Systematic review of randomized controlled trials. Can Fam Phys. 2015;61:e372-81.

Andreae MH, Carter GM, Shaparin N, Suslov K, Ellis RJ, Ware MA, Abrams DI, Prasad H, Wilsey B, Indyk D, Johnson M, Sacks HS. Inhaled cannabis for chronic neuropathic pain: A metaanalysis of individual patient data. Journal of Pain. 2015;16(12):1121–1232. [PMC free article] [PubMed]

Fitzcharles MA, Ste-Marie PA, Hauser W, Clauw DJ, Jamal S, Karsh J, Landry T, LeClercq S, McDougall JJ, Shir Y, Shojania K, Walsh Z. Efficacy, tolerability, and safety of cannabinoid treatments in the rheumatic diseases: A systematic review of randomized controlled trials. Arthritis Care and Research. 2016;68(5):681–688. [PubMed]

Richards BL, Whittle SL, Van Der Heijde DM, Buchbinder R. Efficacy and safety of neuromodulators in inflammatory arthritis: A Cochrane systematic review. Journal of Rheumatology. 2012;39(Suppl 90):28–33. [PubMed]

Snedecor SJ, Sudharshan L, Cappelleri JC, Sadosky A, Desai P, Jalundhwala YJ, Botteman M. Systematic review and comparison of pharmacologic therapies for neuropathic pain associated with spinal cord injury. Journal of Pain Research. 2013;6:539–547. [PMC free article] [PubMed]