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General

Cannabinoids and Their Role in Chronic Pain Treatment: Current Concepts and a Comprehensive Review

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For decades, chronic pain was managed with an almost conventional approach of using a wide range of analgesic spectrum, surgical approaches and complex interventional pain techniques to modulate or even interrupt pain pathways. These different approaches carry many pharmacological hazards together with the lack of efficacy and safety of many interventional and surgical management techniques for chronic pain have mandated searching for other effective therapies including alternative treatments. Cannabinoids are naturally occurring substances that are derived from Cannabis sativa L. The usage of cannabinoids and their related synthetic chemical compounds has emerged as a choice in the management of different chronic pain conditions is being evaluated, however, the efficacy is still not consistently established. In the present investigation, therefore, we discuss the different aspects related to cannabinoids and their implications in the management of chronic pain conditions. This review will also discuss the safety profile of the cannabinoids together with the legal considerations that hinder their use in different countries.

INTRODUCTION

Chronic pain is one of the most distressing conditions that may encounter humans throughout life.[1] The American Academy of Pain Medicine has defined chronic pain as pain that lasts longer than the usual course of an acute injury or disease or the pain that recurs for months or years.[2] In 2016, it was estimated that 20.4% (50 million) of American adults are suffering from chronic pain with a bad impact on the quality of life for 8.0% of them.[3] According to the 11th revision of the International Classification of Diseases (ICD11), chronic pain has been classified into different categories regarding the etiological background present in each condition. For instance, chronic pain may be caused by musculoskeletal abnormalities, advanced malignancy, postsurgical complication, visceral pain, and many different pain conditions.[4]

For decades, chronic pain was managed with an almost conventional approach of using a wide range of analgesic spectrum, ranging from non-steroidal anti-inflammatory drugs (NSAIDs) to week and strong opioid agonists.[5] The difficulty and challenges in the management of chronic pain has raised another consideration of using surgical approaches and complex interventional pain techniques to modulate or even interrupt pain pathways.[6] In this regard, many of the current treatments include the potential of adverse events, including opioid mediated overdose and failure of effective response to injections and to advanced interventional pain therapy techniques. In the United States, chronic use of NSAIDs, which taken chronically can cause asymptomatic gastrointestinal bleeding, has proven to cause nearly 103,000 hospitalizations and 16,500 deaths annually, which is surprisingly comparable to the statistics coming from other well-known disease states and conditions like acquired immune deficiency syndrome (AIDS), asthma, and others.[7] These risks are conventionally attributed to not only increasing incidence of gastrointestinal bleeding but as well, chronic kidney disease.[8,9] At present, there is a tragic opioid epidemic, and this is largely understood through different opioid medications stopped natural opioid endogenous production, making people taking long term opioids physically dependent on these exogenous agents, and when stopped, many of these people will pursue opioids that are laced with impurities and fentanyl, include heroin, and other agents that cause respiratory depression and death. In the US, this past year, there were over 83,000 opioid related deaths.[10,11]

Common side effects of opioid administration include sedation, dizziness, nausea, vomiting, constipation, physical dependence, tolerance, and respiratory depression.[12] Physical dependence and addiction are of particular concern especially in the long-term management of chronic pain conditions. One meta-analysis has reported that the rate of opioid misuse averaged between 21% and 29% and the rate of addiction averaged between 8% and 12% among patients treated with opioids for chronic pain conditions.[13]

These pharmacological hazards together with the lack of efficacy and safety of many interventional and surgical management techniques for chronic pain have mandated searching for other effective therapies including alternative treatments.[14] Cannabinoids are naturally occurring substances that are derived from Cannabis sativa L. (C. Sativa).[15] The usage of cannabinoids and their related synthetic chemical compounds has emerged as a choice in the management of different chronic pain conditions in the last decade.[16] The use of cannabinoids in a wide spectrum of chronic pain conditions is being evaluated, however, the efficacy is still not consistently established.[17–19] In the present investigation, therefore, we discuss the different aspects related to cannabinoids and their implications in the management of chronic pain conditions. This review will also discuss the safety profile of the cannabinoids together with the legal considerations that hinder their use in different countries.

METHODOLOGY

A search of literatures published on PubMed from 2017 to 2021 was conducted using keywords including “cannabis”, “THC”, “CBD”, “Nabiximol”, “cancer”, “non-cancer”, “fibromyalgia”, “neuropathic pain” and “pain”. Many clinical studies that evaluated the effect of THC or CBD on controlling different types of pain were evaluated for a selective review. Findings related to study population, interventions, pain response, and side effects were reviewed, summarized, and are presented in Table (1).

PHARMACOKINETICS OF THE CANNABINOIDS

Cannabis describes three separate forms, e.g., herbal cannabis, ‘hemp’ products, pharmaceutical-grade regulated cannabinoid-based medical products (CBMP). Cannabis sativa which is the plant form contains hundreds of chemical entities known as phytocannabinoids including Δ9-tetrahydrocannabinol (THC), and cannabidiol (CBD) in which have been discovered in the 1960s as the most prevalent bioactive compounds inside cannabis.[20] Then they have been extracted and used in different concentrations to formulate many drugs. Effects like impaired memory, learning, motor function, temperature regulation, and psychosis have limited the use of Cannabis sativa in clinical practice.[20]

The pharmacokinetics of THC and CBD and their effects depend on the formulation and route of administration.[21] The routes of cannabis-based medical uses include smoking cannabis flowers, vaporizing oil formulations, vaporizing ethanolic liquids, vaporizing dry herbs, oro-mucosal administration, oral ingestion of cannabis extracts or edibles, and syqe inhaler.[22] Oral ingestion limits the consistent absorption of both molecules due to their lipophilic nature, which may lead to poor solubility.[22] The peak serum concentration for oral oil-based medication occurs approximately 1.5 h after ingestion in a standardized oil-based oral cannabinoid formulation and is at low nontherapeutic levels after 5–6 h. This makes the bioavailability from the oral route of approximately 13% and even lower through the oral route (approximately 5%) because of extensive first-pass metabolism.[23]

The syqe inhaler is the most effective delivery method for cannabis-based medicine, it reaches the maximum concentration after 3minules only.[22] Therefore, this emphasizes the importance of the solubilization process of lipophilic drugs such as CBD. These findings offer a standardized oral formulation for the delivery of cannabinoids and contribute data for the growing field of cannabinoid pharmacokinetics.[24] The terminal elimination half-life for oral CBD was approximately 70 h, suggesting that 2-3 weeks are needed to fully eliminate CBD.[25]

THC and CBD are hepatically metabolized, the potential exists for drug interactions via inhibition or induction of cytochrome p450 enzymes or transporters. The metabolism of THC is predominantly hepatic, via cytochrome P450 (CYP 450) isozymes CYP2C9, CYP2C19 and CYP3A4. CBD is also hepatically metabolized, primarily by isozymes CYP2C19 and CYP3A4 and additionally, CYP1A1, CYP1A2, CYP2C9, and CYP2D6. Such pharmacokinetic interactions may occur and care should be taken when prescribing with other hepatically metabolized medications.[20] It has been found that cannabis enhances the analgesic effects of opioids, thereby allowing for lower doses.[26] Both Vulnerable populations, such as older patients, may be at increased risk of adverse effects. There is an overall rarity of studies related to either pharmacokinetic or pharmacodynamic properties for CBMP. Therefore, it is imperative to understand the need to initiate prescribing of CBMP using a ‘start low and go slow’ approach. All patients commenced on CBMP require careful monitoring and observation, particularly the elderly and those with polypharmacy to achieve optimal effects with fewer adverse events.[26]

ANALGESIC EFFECTS OF CANNABIS, MECHANISM OF ACTION

ENDOCANNABINOID SYSTEM

Cannabinoids exert their analgesic effect by manipulating various pain pathways and molecular mechanisms along with different body systems which are now known as the endocannabinoid system.[27] This system includes the whole pathway on which the cannabinoids exert their different actions, including analgesia, from receptors to the transport proteins together with the enzymes responsible for its synthesis and degradation.[28] The analgesic effect of either internal or external cannabinoids has been centered around activation of the activity of 2 receptors named cannabinoids receptor1 (CB1R) and cannabinoid receptor 2 (CB2R).[29] Both receptors are members of G- protein-coupled receptors that are coupled to pertussis toxin (PTX)-sensitive $G_{i/o}$ protein. On activation of this protein, it inhibits the activity of the adenylate cyclase and subsequently the cyclic AMP production.[30] Additionally, CBR1 has been linked to activation of other G-proteins families in both cell-type and ligand-dependent manners.[31] The CB1R is consistently located along the descending and the ascending pain neurons at multiple levels from the

Table 1.

Cannabinoid Receptors and Their Relationship With Chronic Pain: A Narrative Review	role of the cannabinoid system in chronic inflammatory pain.	it reduce burden of chronic pain	Anthony AT, Rahmat S, Sangle P, Sandhu O, Khan S. Cannabinoid Receptors and Their Relationship With Chronic Pain: A Narrative Review. Cureus. 2020 Sep 14;12(9):e10436. doi: 10.7759/cureus.10436. PMID: 33072446; PMCID: PMC7557112.
Use of cannabidiol (CBD) for the treatment of chronic pain	treatment efficacy of CBD, THC,nabiximols for chronic pain and adverse events with each.		Urits I, Gress K, Charipova K, Habib K, Lee D, Lee C, Jung JW, Kassem H, Cornett E, Paladini A, Varrassi G, Kaye AD, Viswanath O. Use of cannabidiol (CBD) for the treatment of chronic pain. Best Pract Res Clin Anaesthesiol. 2020 Sep;34(3):463-477. doi: 10.1016/j.bpa.2020.06.004. Epub 2020 Jul 2. PMID: 33004159.
The Neuroimmunology of Chronic Pain: From Rodents to Humans	neuroimmune signaling mechanisms and novel therapeutic targets in rodent models of chronic pain		Grace PM, Tawfik VL, Svensson CI, Burton MD, Loggia ML, Hutchinson MR. The Neuroimmunology of Chronic Pain: From Rodents to Humans. J Neurosci. 2021 Feb 3;41(5):855-865. doi: 10.1523/JNEUROSCI.1650-20.2020. Epub 2020 Nov 25. PMID: 33239404; PMCID: PMC7880288.
The pharmacokinetics, efficacy, and safety of a novel selective-dose cannabis inhaler in patients with chronic pain: A randomized, double-blinded, placebo-controlled trial	metered-dose cannabis inhaler delivered precise and low THC doses, produced a dose-dependent and safe analgesic effect in patients with neuropathic pain/ complex-regional pain syndrome (CRPS)		Almog S, Aharon-Peretz J, Vulfsons S, Ogintz M, Abalia H, Lupo T, Hayon Y, Eisenberg E. The pharmacokinetics, efficacy, and safety of a novel selective-dose cannabis inhaler in patients with chronic pain: A randomized, double-blinded, placebo-controlled trial. Eur J Pain. 2020 Sep;24(8):1505-1516. doi: 10.1002/ejp.1605. Epub 2020 Jun 12. PMID: 32445190; PMCID: PMC7496774.
Potential Pharmacokinetic Drug-Drug Interactions between Cannabinoids and Drugs Used for Chronic Pain	interactions between cannabinoids and pain medication through drug transporters	morphine,codeine,methadone,tramadol..augment analgesia ...in animals	Vázquez M, Guevara N, Maldonado C, Guido PC, Schaiquevich P. Potential Pharmacokinetic Drug-Drug Interactions between Cannabinoids and Drugs Used for Chronic Pain. Biomed Res Int. 2020 Aug 13;2020:3902740. doi: 10.1155/2020/3902740. PMID: 32855964; PMCID: PMC7443220.
Cannabis Use in Hospitalized Patients with Chronic Pain	Cannabis use increased substantially from 2011 to 2015	it improves chronic pain in CRP,Trauma,post surgical,spondylosis	Orhurhu V, Urits I, Olusunmade M, Olayinka A, Salisu Orhurhu M, Uwandu C, Aner M, Ogunsola S, Akpala L, Hirji S, Viswanath O, Karri J, Simopoulos T, Gill J. Cannabis Use in Hospitalized Patients with Chronic Pain. Adv Ther. 2020 Aug;37(8):3571-3583. doi: 10.1007/s12325-020-01416-9. Epub 2020 Jul 6. PMID: 32632850; PMCID: PMC7370966.

Cannabis Use and Low-Back Pain: A Systematic Review	analgesic for low-back pain	more research regarding their analgesic effect is needed	First L, Douglas W, Habibi B, Singh JR, Sein MT. Cannabis Use and Low-Back Pain: A Systematic Review. Cannabis Cannabinoid Res. 2020 Dec 15;5(4):283-289. doi: 10.1089/can.2019.0077. PMID: 33381642; PMCID: PMC7759283.
Understanding Cannabis-Based Therapeutics in Sports Medicine	treatment for athletes with chronic pain conditions	difficult for the sport medicine clinicia to recommed cbd dt limited research	Maurer GE, Mathews NM, Schleich KT, Slayman TG, Marcussen BL. Understanding Cannabis-Based Therapeutics in Sports Medicine. Sports Health. 2020 Nov/Dec;12(6):540-546. doi: 10.1177/1941738120956604. Epub 2020 Sep 16. PMID: 32936058; PMCID: PMC7785900.
Cannabis and cannabidiol (CBD) for the treatment of fibromyalgia	cannabis in fibromyalgia:risk benefit	its usage is limited	Berger AA, Keefe J, Winnick A, Gilbert E, Eskander JP, Yazdi C, Kaye AD, Viswanath O, Urits I. Cannabis and cannabidiol (CBD) for the treatment of fibromyalgia. Best Pract Res Clin Anaesthesiol. 2020 Sep;34(3):617-631. doi: 10.1016/j.bpa.2020.08.010. Epub 2020 Aug 15. PMID: 33004171.
Analgesic Effects and Impairment in Locomotor Activity Induced by Cannabinoid/Opioid Combinations in Rat Models of Chronic Pain	antinociceptive effect of combining synthetic cannabinoids with subtherapeutic doses of opioids	t WIN55212 in combination with tramadol produced a significant reduction in the nociceptive response	Alsalem M, Altarifi A, Haddad M, Azab B, Kalbouneh H, Imraish A, Saleh T, El-Salem K. Analgesic Effects and Impairment in Locomotor Activity Induced by Cannabinoid/Opioid Combinations in Rat Models of Chronic Pain. Brain Sci. 2020 Aug 6;10(8):523. doi: 10.3390/brainsci10080523. PMID: 32781705; PMCID: PMC7547378.
Consensus-based recommendations for titrating cannabinoids and tapering opioids for chronic pain control	medical cannabis to support opioid tapering	safe introduction and titration of cannabinoids in concert with tapering opioids.	Sihota A, Smith BK, Ahmed SA, Bell A, Blain A, Clarke H, Cooper ZD, Cyr C, Daeninck P, Deshpande A, Ethans K, Flusk D, Le Foll B, Milloy MJ, Moulin DE, Naidoo V, Ong M, Perez J, Rod K, Sealey R, Sulak D, Walsh Z, O'Connell C. Consensus-based recommendations for titrating cannabinoids and tapering opioids for chronic pain control. Int J Clin Pract. 2020 Nov 28:e13871. doi: 10.1111/ijcp.13871. Epub ahead of print. PMID: 33249713.
[Medical cannabinoids and their indications in chronic pain]	Its use is only validated in certain limited cases, in particular spasticity linked to multiple sclerosis and refractory epilepsies. All other prescriptions require a special request to the OFSP	cannabis use is only validated in certain limited cases, in particular spasticity linked to multiple sclerosis and refractory epilepsies. All other prescriptions require a special request to the OFSP. Moreover, cannabinoid intake may produce several dose-dependent side effects	El Faleh-Kayal Y, Suter M, Cachemaille M. Les cannabinoïdes et leurs indications en antalgie chronique [Medical cannabinoids and their indications in chronic pain]. Rev Med Suisse. 2020 Jul 15;16(700):1363-1366. French. PMID: 32672015.

Medical cannabis for orthopaedic patients with chronic musculoskeletal pain: does evidence support its use?	cannabs in chronic musculoskeletl pain	cannabinoids Therapeutic Advances in Musculoskeletal Disease may be considered as an adjunctive therapy after recommended first- and second-line therapies have failed to provide sufficient efficacy or tolerability	Johal H, Vannabouathong C, Chang Y, Zhu M, Bhandari M. Medical cannabis for orthopaedic patients with chronic musculoskeletal pain: does evidence support its use? Ther Adv Musculoskelet Dis. 2020 Jul 2;12:1759720X20937968. doi: 10.1177/1759720X20937968. PMID: 32655704; PMCID: PMC7333482.
Cannabinoids in the Treatment of Back Pain	potential role of cannabinoids in the treatment of back pain.	The significant risk of morbidity, mortality, and dependence secondary to opioid medications have increased the interest in nonopioid medications	Kim TE, Townsend RK, Branch CL, Romero-Sandoval EA, Hsu W. Cannabinoids in the Treatment of Back Pain. Neurosurgery. 2020 Aug 1;87(2):166-175. doi: 10.1093/neuros/nyz573. PMID: 32097466.
Cannabinoid and Opioid Use Among Total Joint Arthroplasty Patients: A 6-Year, Single-Institution Study	total jont arthroplasty pts cannabinoid versus opioid	During a 6-year period, cannabinoid use increased more than 60%, and opioid use decreased approximately 30%.	Denduluri SK, Woolson ST, Indelli PF, Mariano ER, Harris AHS, Giori NJ. Cannabinoid and Opioid Use Among Total Joint Arthroplasty Patients: A 6-Year, Single-Institution Study. Orthopedics. 2021 Jan 1;44(1):e101-e106. doi: 10.3928/01477447-20200928-02. Epub 2020 Oct 1. PMID: 33002174.
Cannabinoid hyperemesis syndrome: definition, pathophysiology, clinical spectrum, insights into acute and long-term management	episodic vomiting	It is characterized by stereotypical episodic vomiting in the setting of chronic, daily cannabis use, with cycles decreasing by the cessation of cannabis	Gajendran M, Sifuentes J, Bashashati M, McCallum R. Cannabinoid hyperemesis syndrome: definition, pathophysiology, clinical spectrum, insights into acute and long-term management. J Investig Med. 2020 Dec;68(8):1309-1316. doi: 10.1136/jim-2020-001564. Epub 2020 Oct 28. PMID: 33115959.
Use of Cannabis for Self-Management of Chronic Pelvic Pain	cannabidiol in chronic pelvic pain	improvement in symptoms, including pain, cramping, muscle spasms, anxiety, depression, sleep disturbances, libido, and irritability.	Carrubba AR, Ebbert JO, Spaulding AC, DeStephano D, DeStephano CC. Use of Cannabis for Self-Management of Chronic Pelvic Pain. J Womens Health (Larchmt). 2020 Nov 16. doi: 10.1089/jwh.2020.8737. Epub ahead of print. PMID: 33252316.
Cannabis: are there any benefits?	herbal:THC,CBD,Medical:CKMB more benefits	CBMP:pharmacology,evidence,SE	Vickery AW, Finch PM. Cannabis: are there any benefits? Intern Med J. 2020 Nov;50(11):1326-1332. doi: 10.1111/imj.15052. PMID: 33215831.
Cannabinoid use among Americans with MS: Current trends and gaps in knowledge	THC and CBD in MS	Benefit from cannabinoids for sleep and pain were strongly correlated (r ¼ 0.65, p < 0.0001)	Braley TJ, Whibley D, Alschuler KN, Ehde DM, Chervin RD, Clauw DJ, Williams D, Kratz AL. Cannabinoid use among Americans with MS: Current trends and gaps in knowledge. Mult Scler J Exp Transl Clin. 2020 Sep 22;6(3):2055217320959816. doi: 10.1177/2055217320959816. PMID: 33014410; PMCID: PMC7518014.

Current application of cannabidiol (CBD) in the management and treatment of neurological disorders	anxiety, chronic pain, trigeminal neuralgia, epilepsy, and essential tremors as well as psychiatric disorders>>>>Cannabidiol	CBD has shown promise in the treatment of neurological disorders such as anxiety, chronic pain, trigeminal neuralgia, epilepsy, and essential tremors as well as psychiatric disorders	Fiani B, Sarhadi KJ, Soula M, Zafar A, Quadri SA. Current application of cannabidiol (CBD) in the management and treatment of neurological disorders. Neurol Sci. 2020 Nov;41(11):3085-3098. doi: 10.1007/s10072-020-04514-2. Epub 2020 Jun 16. PMID: 32556748.
Analgesic Effects of Cannabinoids for Chronic Non-cancer Pain: a Systematic Review and Meta-Analysis with Meta-Regression	cannabiinoids in neuropathic versus non neuropathic pain	mean pain score (scale 0-10) reduction of -0.70 ($p < 0.001$, random effect). Meta-regression showed that analgesic efficacy was similar for neuropathic and non-neuropathic pain (Difference = -0.14, $p = 0.262$	Wong SSC, Chan WS, Cheung CW. Analgesic Effects of Cannabinoids for Chronic Non-cancer Pain: a Systematic Review and Meta-Analysis with Meta-Regression. J Neuroimmune Pharmacol. 2020 Dec;15(4):801-829. doi: 10.1007/s11481-020-09905-y. Epub 2020 Mar 14. PMID: 32172501.
CBD for the treatment of pain: What is the evidence?	why CBD IS better	there is insufficient evidence to recommend CBD for the treatment of pain	Svensson CK. CBD for the treatment of pain: What is the evidence? J Am Pharm Assoc (2003). 2020 Nov-Dec;60(6):e80-e83. doi: 10.1016/j.japh.2020.06.009. Epub 2020 Jul 4. PMID: 32636158.
Cannabinoids in multiple sclerosis: A neurophysiological analysis	oral spray containing delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) in MS	The THC-CBD spray improved spasticity and pain in secondary progressive MS patients.	Vecchio D, Varrasi C, Virgilio E, Spagarino A, Naldi P, Cantello R. Cannabinoids in multiple sclerosis: A neurophysiological analysis. Acta Neurol Scand. 2020 Oct;142(4):333-338. doi: 10.1111/ane.13313. Epub 2020 Jul 21. PMID: 32632918.
Neuropharmacological Effects of the Main Phytocannabinoids: A Narrative Review	mechanisms of action of the phytocannabinoids, especially THC and CBD. the indications and adverse effects	THC acts as a partial agonist at cannabinoid 1/2 receptors (CB1/2). It is responsible for the characteristic effects of cannabis, such as euphoria, relaxation, and changes in perceptions. THC can also produce dysphoria, anxiety, and psychotic symptoms. . CBD acts as a noncompetitive negative allosteric modulator of the CB1 receptor, as an inverse agonist of the CB2 receptor, and as an inhibitor of the reuptake of the endocannabinoid anandamide.. CBD does not produce the typical effects associated with THC.	Dos Santos RG, Hallak JEC, Crippa JAS. Neuropharmacological Effects of the Main Phytocannabinoids: A Narrative Review. Adv Exp Med Biol. 2021;1264:29-45. doi: 10.1007/978-3-030-57369-0_3. PMID: 33332002.
Antinociception mechanisms of action of cannabinoid-based medicine: an overview for anesthesiologists and pain physicians	cannabinoids' diverse mechanisms of action as it pertains to nociception modulation	Cannabinoids-opioids cross-modulation and synergy contribute significantly to tolerance and antinociceptive effects of cannabinoids. ' cb diverse mechanisms of action as it pertains to nociception modulation	Narouze S. Antinociception mechanisms of action of cannabinoid-based medicine: an overview for anesthesiologists and pain physicians. Reg Anesth Pain Med. 2021 Mar;46(3):240-250. doi: 10.1136/rapm-2020-102114. Epub 2020 Nov 25. PMID: 33239391.
Medical cannabis and cognitive performance in middle to old adults treated for chronic pain	long-term medical cannabis (MC) use and cognitive function	whole plant MC does not have a widespread impact on cognition in older chronic pain patients	Sznitman SR, Vulfsons S, Meiri D, Weinstein G. Medical cannabis and cognitive performance in middle to old adults treated for chronic pain. Drug Alcohol Rev. 2021 Feb;40(2):272-280. doi: 10.1111/dar.13171. Epub 2020 Sep 22. PMID: 32964502.

Sex differences and the endocannabinoid system in pain		Female rodents have generally been found to be more sensitive to the effects of Δ9-THC	Blanton HL, Barnes RC, McHann MC, Bilbrey JA, Wilkerson JL, Guindon J. Sex differences and the endocannabinoid system in pain. Pharmacol Biochem Behav. 2021 Mar;202:173107. doi: 10.1016/j.pbb.2021.173107. Epub 2021 Jan 12. PMID: 33444598; PMCID: PMC8216879.
Tetrahydrocannabinol and Cannabidiol Use in an Outpatient Palliative Medicine Population	THC and CBD in palliative	Approximately a quarter of outpatient palliative care patients use THC or CBD, often on a daily basis.	Highet BH, Lesser ER, Johnson PW, Kaur JS. Tetrahydrocannabinol and Cannabidiol Use in an Outpatient Palliative Medicine Population. Am J Hosp Palliat Care. 2020 Aug;37(8):589-593. doi: 10.1177/1049909119900378. Epub 2020 Jan 27. PMID: 31986898.
Ingestion of a THC-Rich Cannabis Oil in People with Fibromyalgia: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial	thc rich oil in fibromyalgia	the cannabis group presented a statistically significant reduction, going from 75.5 to 30.5 points (P< 0.001). At the same time, the placebo group maintained its score (P¼ 0.07). Furthermore, in an isolated analysis of FIQ items, the cannabis group presented a reduction in mean values on the “feel good,” “pain,” and “fatigue” items. The placebo group presented a reduction in mean values on the “depression” item	Chaves C, Bittencourt PCT, Pelegrini A. Ingestion of a THC-Rich Cannabis Oil in People with Fibromyalgia: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial. Pain Med. 2020 Oct 1;21(10):2212-2218. doi: 10.1093/pm/pnaa303. PMID: 33118602; PMCID: PMC7593796.
The cannabinoid CB 2 receptor agonist LY2828360 synergizes with morphine to suppress neuropathic nociception and attenuates morphine reward and physical dependence	synergy with morphine	cannabinoid CB2 receptor activation enhances the therapeutic properties of opioids while attenuating unwanted side-effects such as reward and dependence that occur with sustained opioid treatment.	Iyer V, Slivicki RA, Thomaz AC, Crystal JD, Mackie K, Hohmann AG. The cannabinoid CB2 receptor agonist LY2828360 synergizes with morphine to suppress neuropathic nociception and attenuates morphine reward and physical dependence. Eur J Pharmacol. 2020 Nov 5;886:173544. doi: 10.1016/j.ejphar.2020.173544. Epub 2020 Sep 5. PMID: 32896549; PMCID: PMC7694697.
Cannabinoids in chronic non-cancer pain medicine: moving from the bench to the bedside			Meng H, Deshpande A. Cannabinoids in chronic non-cancer pain medicine: moving from the bench to the bedside. BJA Educ. 2020 Sep;20(9):305-311. doi: 10.1016/j.bjae.2020.05.002. Epub 2020 Jul 21. PMID: 33456965; PMCID: PMC7807923.
Emerging Promise of Cannabinoids for the Management of Pain and Associated Neuropathological Alterations in Alzheimer's Disease	cannabinoid in alzheimer disease	Cannabinoids act by targeting several signaling processes, such as pain, abnormal processing of Ab and tau, neuroinflammation, excitotoxicity, oxidative stress, and mitochondrial dysfunction, which play a pivotal role in the management of AD. Cannabinoids also ameliorate behavioral and cognitive dysfunctions. T	Uddin MS, Mamun AA, Sumsuzzman DM, Ashraf GM, Perveen A, Bungau SG, Mousa SA, El-Seedi HR, Bin-Jumah MN, Abdel-Daim MM. Emerging Promise of Cannabinoids for the Management of Pain and Associated Neuropathological Alterations in Alzheimer's Disease. Front Pharmacol. 2020 Jul 22;11:1097. doi: 10.3389/fphar.2020.01097. PMID: 32792944; PMCID: PMC7387504.

Cannabis for Chronic Pain: A Rapid Systematic Review of Randomized Control Trials		This review concludes that cannabinoids may have a potential role in chronic pain management	Longo R, Oudshoorn A, Befus D. Cannabis for Chronic Pain: A Rapid Systematic Review of Randomized Control Trials. Pain Manag Nurs. 2021 Apr;22(2):141-149. doi: 10.1016/j.pmn.2020.11.006. Epub 2021 Jan 19. PMID: 33353819.
General risks of harm with cannabinoids, cannabis, and cannabis-based medicine possibly relevant to patients receiving these for pain management: an overview of systematic reviews		harms associated with cannabis and cannabinoids generally relevant to individuals being treated for pain. including psychiatric and psychosocial harms, cognitive/behavioral effects, motor vehicle accidents, cardiovascular, respiratory, cancer-related, maternal/fetal, and general harms	Mohiuddin M, Blyth FM, Degenhardt L, Di Forti M, Eccleston C, Haroutounian S, Moore A, Rice ASC, Wallace M, Park R, Gilron I. General risks of harm with cannabinoids, cannabis, and cannabis-based medicine possibly relevant to patients receiving these for pain management: an overview of systematic reviews. Pain. 2021 Jul 1;162(Suppl 1):S80-S96. doi: 10.1097/j.pain.0000000000002000. PMID: 32941319.
The Impact of Medical Cannabis on Intermittent and Chronic Opioid Users with Back Pain: How Cannabis Diminished Prescription Opioid Usage	cannabis and opioids	cannabis use worked as an alternative to prescription opioids in just over half of patients with low back pain and as an adjunct to diminish use in some chronic opioid users.	Takakuwa KM, Hergenrather JY, Shofer FS, Schears RM. The Impact of Medical Cannabis on Intermittent and Chronic Opioid Users with Back Pain: How Cannabis Diminished Prescription Opioid Usage. Cannabis Cannabinoid Res. 2020 Sep 2;5(3):263-270. doi: 10.1089/can.2019.0039. PMID: 32923663; PMCID: PMC7480723.

peripheral neuronal terminal to the supraspinal level including the dorsal root ganglion, a critical relay station for pain neuronal pathway. Unlike CB1R, CB2R has been strongly recognized as both peripheral and central cannabinoids receptor that is located within the numerous peripheral tissue types within a recognizable expression on the inflammatory cells.[32–34] The location of the CB2R on the nervous system has been linked to the pain-related areas including the cerebral cortex, hippocampus, striatum, amygdala, and thalamic nuclei.[28,35] One of the basic mechanisms by which the different cannabinoids receptors exert their analgesic effect is through modulation of pain impulse transmission through modifying the release of the neurotransmitter at the synaptic cleft.[27] For instance, 2, acyl glycerol (2-AG) which is one of the internal cannabinoids, is usually synthesized as a response to increased intracellular calcium. Upon production, it is transported retrogradely to interact with the presynaptic cannabinoid's receptors.[27,36] When activated, CB1R suppresses the release of the chemical neurotransmitters through inactivating the presynaptic voltage-gated calcium channels and inhibition of the adenylate cyclase.[36,37]

NON-CANNABINOIDS RECEPTOR EFFECTS

Besides ameliorating pain by interaction with CB1R and CB2R, it has been shown that cannabinoids can carry out their analgesic effect through other non-CB1R / CB2R G protein-coupled receptors.[38,39] These other G-protein coupled receptors include opioid and serotonin receptors.[40,41] Additionally, O'Sullivan has reported that cannabinoids can exert nuclear effects through the modulation of peroxisome proliferator-activated receptors (PPARs).[42] More recently, multiple studies have demonstrated the potential role of cannabinoids in activating the membrane ion channels, specifically transient receptor potential channels (TRP).[43,44]

ANTI-INFLAMMATORY EFFECTS

In addition to the abovementioned neuronal effects, a piece of growing evidence suggests that the analgesic effect may be also attributed to its action on the process of inflammation itself.[45,46] The anti-inflammatory effect of cannabinoids, hence analgesic, is attributed to the multiple mechanisms that affect the different aspects of the process of inflammation. Indeed, ablation of CB2R on a colitis animal model has shown an increase in the inflammatory activity within the macrophage.[47] The exaggeration of the inflammatory effect was similarly noted in encephalomyelitis after knocking down the CB2R.[48] Additionally, cannabinoids have also been reported to decrease the production of inflammatory cytokines by interfering with the action of inflammasome and inducing autophagy of the inflammatory cells.[49] In the last decades, many studies have demonstrated that tetrahydrocannabinol is 80 times more potent than aspirin and two times more hydrocortisone in decreasing the inflammatory reaction.[50,51] Cannabinoids have also demonstrated enhancement of the apoptosis of the inflammatory cells through activation of caspases upon binding to their respective receptors.[52] Similarly, it has also been shown to decrease the expression of major histocompatibility molecules on the surface of the splenic dendritic cells.[53] The cannabinoids have also been shown to decrease the production of inflammatory cytokines such as IL-6 that is readily implicated in multiple autoimmune conditions such as systemic lupus erythematosus and rheumatoid arthritis.[54] Additionally, cannabinoids have also demonstrated inhibitory activity against LPS-stimulated mRNA expression of IL-1α, IL-1β, IL-6, and TNF-α in cultured microglial cells of a rat.[55]

Therefore, it's imperative to understand that the analgesic effect of the cannabinoids may be strongly attributed to modulating both ascending and descending pain pathways together with strongly suppressing the associated inflammation in multiple chronic pain conditions. The mechanism of suppressing the inflammatory process may be attributed to a decrease in the production of inflammatory cytokines, suppression of the inflammatory implicated enzymes and even inducing apoptosis of the inflammatory cells.

POTENTIAL USES OF MEDICAL CANNABIS IN PAIN MANAGEMENT

CANNABINOIDS AND NEUROPATHIC PAIN

Neuropathic pain may be due to small nerve fiber involvement as in diabetes, or nerve impingement like radiculopathy or sciatica. There are many standard medical therapies for the management of neuropathic pain. However, THC-oromucosal spray or oil showed a beneficial impact even in refractory cases.[56]

A randomized controlled study was conducted on Seventeen patients with chronic lumbar radicular pain who were assigned to receive either THC oil or placebo oil. The study showed a significant reduction in the pain in the THC group compared to the placebo group. THC-induced analgesia was correlated with a reduction in functional connectivity between the anterior cingulate cortex(ACC) and the sensorimotor cortex.[57] In addition, Xu et al. conducted another randomized, placebo-controlled trial involving 29 patients with peripheral neuropathy of different etiologies. The patients were randomly divided to receive either cannabis oil or emu oil for 4 weeks, then the cases group are allowed to cross over and receive the placebo. There was a statistically significant reduction in intense pain, sharp pain, cold and itchy sensations in the CBD group when compared to the placebo. However, the deep pain showed statistically insignificant improvement.[58]

Regarding multiple sclerosis, Amerongen et al conducted a double-blind, placebo-controlled, crossover trial including 24 patients who have progressive multiple sclerosis with moderate spasticity. Spasticity and pain appear to be influenced by D9-THC through higher-level central nervous system modulation of perception of spasticity rather than electrophysiologic muscle spasticity itself. Accordingly, ECP002A(which is an oral formulation of d THC) may have a role in the symptomatic treatment of spasticity and pain in multiple sclerosis.[59]

CANNABINOIDS IN CANCER PAIN

Cancer pain affects the quality of patients' life and represents a major economic burden across the world. Unfortunately, opioid therapy and other conventional analgesic modalities don't show complete relief of pain in many patients. Various studies have been conducted to evaluate the potential use of CBD and nabiximol in cancer patients.[56] A study conducted in 2018 by Lchtman et al., assessed using the oral spray of Nabiximol in advanced cancer patients with chronic pain.[60] They included the patients with average pain Numerical Rating Scale scores ⩾4 and ⩽8 despite optimized opioid therapy. They found a median percent improvement in average score in the nabiximol group 10.7 versus 4.5% in the placebo group. Moreover, Nabiximol was statistically superior to placebo on two of three quality-of-life instruments which advocated its usage in patients with early tolerance to opioid therapy.

CANNABINOIDS IN OSTEOARTHRITIS

In a randomized placebo-controlled, double-blinded study conducted on a spontaneous canine model of osteoarthritis, Verrico et al found that CBD significantly decreased pain and increased mobility in a dose-dependent fashion among animals.[61]

CANNABIS IN FIBROMYALGIA

Fibromyalgia is characterized by multifocal points of pain, a sense of fatigue, and psychiatric symptoms like depression. Although many studies showed improvement of the symptoms after cannabis use, no clinical evidence regarding its use at the time being.[62] Tine van et al., assessed the short-term analgesic effects of inhaled pharmaceutical-grade cannabis in 20 chronic pain patients with fibromyalgia. They tested three different cannabis (Bedrocan, Bediol, and Bedrolite) with different concentrations of THC and CBD versus placebo on the different pain stimuli.[63] They found none of the active treatments were effective in reducing spontaneous pain scores more than placebo. However, the. Group of Bediol (which contains a high concentration of THC) displayed a 30% decrease in spontaneous pain scores compared to placebo (90% vs 55% of patients, P50.01). Therefore, further studies are needed to determine the long-term treatment effects on pain score and investigate the THC–CBD interactions.

On the other hand, a multicenter, double-blind, randomized, placebo-controlled, parallel-group study proved the benefit of THC-rich cannabis oil (24.44 mg/mL of THC and 0.51mg/mL of cannabidiol [CBD]) on symptoms and quality of life of patients who have fibromyalgia in Brazil. In this study, 20 patients with fibromyalgia were randomly assigned to take either cannabis oil or olive oil. After 8 weeks, the cannabis group presented a significant decrease in FIQ (Fibromyalgia Impact Questionnaire) score in comparison with the placebo group (P<0.001). The more interesting finding is that the cannabis group presented a significant improvement on the "feel good," "pain," "do work," and "fatigue" scores, which promote using cannabis as a herbal medicine option for the treatment of fibromyalgia.[20]

SIDE EFFECTS

CARDIOVASCULAR SYSTEM

Tachycardia and hypertension are the most frequently reported Cardiovascular side effects of cannabinoids while bradycardia and hypotension are rarely reported in 116 patients studied.[64] Three clinical trials stated dose-dependent increases in heart rate but two of them stated a decrease in blood pressure: one in systolic pressure and the other one in diastolic pressure.[65–67] However, one of the disadvantages is the low number of participants in these clinical trials. Another cohort of 7500 Australians estimated a significant 2.3-fold increase in stroke risk in Cannabis users.[68] Moreover, a French cohort declared a significant Association between cannabis use and multifocal intracranial stenosis.[69]

The assessment of lifetime cannabis use and dose-response effects found no association with cardiovascular mortality, stroke, and coronary heart disease.[70] Although weekly cannabis use has been associated with an increased risk for cardiovascular mortality, there is no evidence for an increase in all-cause mortality.[64,70,71] Finally, Atrial fibrillation after cannabis smoking was reported and Buerger disease, a rare form of arteritis, may be linked with cannabis use.[72,73]

RESPIRATORY SYSTEM

The risk of Cough, sputum production, wheezing, dyspnea, and bronchitis increase in cannabis smokers.[74] In addition, many cases of emphysema, chronic obstructive lung disease (COPD), and lung hyperinflation were found with insufficient evidence of obstructed airflow.[75] Moreover, chest tightness, phlegm production, and pulmonary infections such as tuberculosis, legionnaires disease, aspergillosis, and other opportunistic infections may be associated with cannabis smoking.[74,75] Bronchial biopsies showed precancerous lung changes such as increased mitotic activity, squamous cell metaplasia, and columnar cells are indicated in non–tobacco-smoking cannabis smokers.[76] There is no conclusive evidence about lung bullae in cannabis smokers and airway hyperactivity or lung function in long-term cannabis smoking.[77,78]

PSYCHIATRIC DISORDERS

The risk of suicidal ideation behavior, suicide attempt, and suicide death are increased with the use of cannabinoids.[79,80] Cannabis use also increases the psychosis risk and reduces its onset age by about 2.7 years.[81–83] Psychotic-like events are associated with cannabis in a dose-response manner inducing the risk of schizophrenia.[84,85] Moreover, cannabis use is associated with aggravating the severity of symptoms, and less Remission depression, mania, panic or social phobia, post-traumatic stress disorder, and anxiety.[86]

Many systematic reviews and meta-analyses have stated neurocognitive impairment with cannabis use including reasoning, association, flexibility, speed of information processing, verbal memory, language, motor inhibition, conceptual set-shifting, attention, working memory, learning impairments, visuospatial abilities, motor functioning, executive function/abstraction, verbal immediate recall, verbal delayed recall, verbal recognition, prospective memory, total memory, visual learning, verbal learning, prospective event-based and time-based Memories, forgetting, perceptual-motor and reaction time.[86–95]

CARCINOGENIC SIDE EFFECTS

Cannabis use increases the risk of non-seminoma testicular germ cell tumor (TGCT), and with insufficient evidence, oral, Pharyngeal, lung, and esophageal cancers.[96,97] However, some studies showed no increased risk of head and neck cancer, anal, penile, seminoma-TGCT, non-Hodgkin lymphoma, colorectal, or overall cancer. However, an increased risk for primary glioma, cervical, testicular, prostate, bladder, and oropharyngeal cancer, was proved in non–tobacco-smoking cannabis users. In addition, increased risks of childhood leukemia, astrocytoma, rhabdomyosarcoma, and neuroblastoma were weakly associated with parental use of cannabis, In pediatric cancers.[98–100]

MATERNAL AND FETAL SIDE EFFECTS

There is no clear strong evidence about the prenatal side effects of cannabis use. However, prenatal cannabis use seems to have potentially harmful effects on neuropsychological functioning.[101] Moreover, a meta-analysis indicated low birth weight as a side effect of prenatal cannabis use.[102] Other studies related reduced neonatal length, gestational age, head circumference, longer stay neonatal intensive care unit, and maternal anemia to using cannabis.[103]

SYNTHETIC CANNABINOID (SC) SIDE EFFECTS

Many studies have shown different adverse effects linked to SC intoxication. These effects include impairments in motor functioning, attention and response inhibition, impairments in working memory, long-term memory.[104] Moreover, the adverse effects may involve hypertension, tachycardia, nausea, vomiting agitation, seizures, hallucinations, delusions, psychosis, hypokalemia, abdominal pain, hyperglycemia, and leukocytosis.[105–107] Other studies have found an association between kidney damage and SC use.[107] The SC-induced renal impairment may include acute interstitial nephritis, acute tubular necrosis, rhabdomyolysis, Chronic use may lead to severe prerenal azotemia.[108]

CANNABIS ADDICTION

Cannabinoid abuse has increased concomitantly with the growing legalization of cannabis use worldwide. Long-term cannabinoid use (especially if started at a young age) may cause addiction which results in withdrawal syndrome with stopping the chronic cannabinoid use.[109] Diagnostic and Statistical Manual of Mental Disorders (DSM–5) defined Cannabis use disorder as a pathological pattern including tolerance, social and control impairment, and physiological adaptation. Cannabis withdrawal symptoms are like tobacco withdrawal symptoms including depression, anger, irritability, difficulty sleeping, and decreased appetite. These symptoms have been presented after one or two days of Cannabis use stoppage and may last to two weeks.[110–112] These symptoms' intensity varies according to the amount and the potency of cannabis use before discontinuation. Mild to moderate symptoms can be managed in the outpatient detoxification settings reserving hospitalization for severe symptoms.[113] Many modalities have been studied to treat cannabis withdrawal symptoms. Cannabidiol is an aspiring treatment for the withdrawal syndrome because of its safety, tolerability, pharmacological effects on endocannabinoids (inhibit endocannabinoids hydrolysis and reuptake), and interaction with tetrahydrocannabinol effects. A clinical trial has stated that cannabidiol doses (400 and 800 mg) as effective safe doses to reduce cannabis use.[114] Nicotine patches, a 7 mg dose, showed the ability to reduce the withdrawal symptoms in patients with cannabis use disorder who are not nicotine dependent or not heavy cannabis users.[115]

In addition, exogenous progesterone may reduce the withdrawal symptoms in women with acute symptoms as it reduces cannabis craving. However, long-term-large studies are required to approve its use.[116] Although oral tetrahydrocannabinol, lofexidine, nabiximols, and nefazodone reduced depressed mood, anxiety, sleep disorders, and craving, these drugs worsened some withdrawal symptoms as irritability.[117,118] Till now, the main approach to treat the withdrawal symptoms of cannabis use is the psychotherapeutic techniques with no approved drugs for the treatment of cannabis dependence.[119]

LEGAL ISSUES OF CANNABIS

Globally, Cannabis legalization has supporters who believe that it will improve public health, reduce criminal justice expenditure, and stimulate the economy. On the other hand, critics see that the legalization will increase cannabis use affecting health and safety, reducing the educational achievement of teens, and increasing crime.[120] Food and Drug Administration (FDA) has approved only a cannabis-derived drug (Epidiolex (cannabidiol)) and three synthetic cannabis (Marinol and Syndros (dronabinol) and Cesamet (nabilone)). Also, FDA classified cannabis in Schedule I which contains substances with high potentials for abuse. Consequently, conducting cannabis-related clinical trials is complicated. Also, medical-based cannabis and cannabinoids use must be only in necessity and supervised by medical staff.[121,122]

In the USA, Cannabis use is federally Illegal. However, nine states have legalized recreational cannabis use for adults since 2012. Also, Canada legalized medical-based cannabis use in 1999 and recreational use in 2018. In 2019,

The UK legalized medical-based cannabis use in addition to many other countries. Consequently, this should encourage conduction more studies to understand the effect of cannabis in pain management.[123–126]

CONCLUSION

Cannabinoids and their related chemical compounds may play a substantial role in managing different types of chronic pain. Being a natural product with many routes of administration may raise it as a potential alternative for various pain conditions. The cannabinoids related compounds exert their effects by the diverse and versatile mechanisms of action that include both the neuronal and inflammatory pathways. cannabinoids have been studied in different cases of chronic pain with considerable tolerability. However, there was inconsistent efficacy endpoint that mandate further studies to estimate the actual efficacy of cannabinoids in the management of chronic pain disorders. Cannabinoid's usage was also associated with adverse effects. Addiction among the treated patients is still the major concern especially when the doses are adjusted by the medical profession. This hazard raises a strong legal consideration of a wide application of the cannabinoids related compounds in the management of chronic pain. Therefore, its imperative to discuss social, legal, and medical aspects to weigh public risks and concerns related to the usage of cannabinoids in comparison to the expected benefits on the patient's quality of life.

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