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Trigeminal Neuralgia and Cannabidiol Approach: Mini Review

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ABSTRACT

Chronic pain has been managed for decades, mainly by therapies based on a wide spectrum of analgesic drugs, surgical protocols and complex interventions aimed at interfering with pain outcomes or to, at least, modulate it. Unfortunately, all these techniques lead to several pharmacological hazards, besides their lack of efficacy and safety to treat chronic pain. This scenario justified the need of research focused on finding alternative treatments. Cannabinoids are naturally occurring substances deriving from *Cannabis sativa* L. The use of cannabinoids and their metabolites, mainly cannabidiol (CBD), emerged as option to manage different chronic pain conditions. The present review focuses on the CBD mechanism acting in chronic pain conditions, mostly on its specific use to treat trigeminal neuralgia. This review also discusses CBD's safety and interaction with drugs prescribed for neuropathic orofacial pain, mainly Gabapentin/CBD interactions.

Keywords: Cannabidiol, Trigeminal neuralgia, Pain, Gabapentin

Introduction

Overall, there is consensus on the definition of orofacial pain: chronic pain in the head, face and/or neck, which is related to nervous system dysfunction or primary lesion. Unfortunately, the prompter mechanisms of several orofacial pain statuses have not been fully understood, so far, but in many cases, it presents important neuropathic pain elements that do not have any lesion typical of facial structures. However, nerve lesion clearly comes along with pain and burning/knife/electric-shock like responses. Usual disorders inducing neuropathic orofacial pain (NOP) include conditions, such as persistent idiopathic facial pain (PIFP), burning mouth syndrome (BMS), postherpetic neuralgia (PHN) and trigeminal neuralgia (TN) (Clark and Kotteeswaran, 2021).

A review about cannabinoids use and their related synthetic chemical compounds was carried out by Shehata *et al.*, (2022). It was an important approach to the herein addressed conditions. The aforementioned authors have stated that this field has emerged as alternative to monitor and control

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different chronic pain conditions. However, it remains inconsistently established due to reduced outcomes linked to this topic. Shehata *et al.*, (2022) also discussed cannabinoids' safety profile, as well as the legal considerations hindering their use in different countries.

Trigeminal neuralgia (TN) interferes with basic human conditions, such as psychological, physical and social behaviors, since it affects simple touches on the face and mouth movements (Durán *et al.*, 2023). All these effects are reported in epidemiological research focused on pointing out increased depression, anxiety and insomnia caused by these conditions. Important progress in TN symptomatology, pathophysiology, etiology and therapy was observed in the last 10 years, and it was outspread to clinicians and soon turned into clinical practice (Gambeta *et al.*, 2020; Abd-Elsayed, 2020; Kuffler and Foy, 2020; Schiavone and Ziccardi, 2021). Conventional Magnetic Resonance Imaging (MRI) outcomes have shown neurovascular link correlation to morphological changes in the trigeminal nerve, and it points towards TN denoting side. Studies using diffusion tensor imaging were among the important updates in this field. This procedure disclosed the disruption of the trigeminal nerve's microstructure due to demyelination/dysmyelination. Accordingly, the International Association for the Study of Pain (IASP) and the International Headache Society (IHS) developed a new TN classification system (Bendtsen *et al.*, 2020).

Although these outcomes are quite important, the pain-production mechanism remains controversial. Some TN hypotheses deal with the idea that it is caused by peripheral nervous frame deterioration caused by damage in the trigeminal root. Another hypothesis lies on the fact that peripheral nerve damages or trigeminal nerve diseases increase afferent damages due to nerve impulses' electrical conduction across a connection between two neurons where there is a small gap to be crossed by the nerve impulse, which is helped by the neurotransmitter (ephase) to do so, without neurotransmitter mediation (ephaptic transmission). This gap is observed in the middle of afferent unmyelinated axons and non-totally damaged myelinated axons (Doss, 2012). Then, one can observe ganglion cells' retrograde decay and a defective central suppressor mechanism. All these episodes, such as trigeminal root inflammation due to blood vessel or/and aneurysm, happened at pons' level. A demyelination area can be the reason for the aforementioned condition, just as it happens in multiple sclerosis cases (Doss, 2012; Kaufmann and Patel, 2001; UPMC, 2021).

Statistics show 3%-5% prevalence after damages in the peripheral branches of the trigeminal nerve after implants, third molar extraction, orthognathic surgery, mid-face rupture or root canal surgery. These conclusions define the painful traumatic trigeminal neuropathy (PTTN) (Zarembinski and Omrani, 2019).

Overall, the therapy of trigeminal neuropathic pain (TNP) deals with several medicinal and surgical processes. Plasma-Rich Platelets (PRP) can be used to treat many nerve injury stages in the body, as described in many reports (Durán *et al.*, 2023),

Interestingly, some factors have helped best understanding TN pain, among them, saliva from TN individuals showed lower Ang2 (Angiopoietin-2), bFGF (basic fibroblast growth factor), HGF (hepatocyte growth factor), SCF (stem cell factor) and TGF-α (transforming growth factor alpha), and VEGF growth factor levels and higher IL-1β, TNF-α (tumor necrosis factor-alpha), CCL2 (C-C motif chemokine ligand 2), IL-6, IL-17A, and CXCL8 cytokine levels, as well as upper expression doses of chemokine receptors, such as C-C chemokine receptor type 1 (CCR1) CCR2 (CD192), (CD191), CR3 (CD11b), CCR5 (CD196) and CXCR5 (CD185). Patil and Testarelli (2021) suggested that, despite their research's limitations, it was possible achieving high inflammatory interleukins and chemokines' levels. Therefore, their receptors might play key role in pain pathogenesis. Growth factors' decreased expression was likely related to TN neuronal degeneration. More detailed studies are needed to assess and validate these TN-monitoring biomarkers, to get to further progress in drug targets aimed at monitoring and controlling this disease (Patil and Testarelli, 2021).

Analgesic Role of Cannabinoids

TN clinical expressions are hard to diagnose and treat due to their complexity and to the poor understanding of their etiology and pathogenesis. Common pain management strategies associate pharmacological medication with supplementary, non-pharmacological therapies (Minervini *et al.*, 2018, 2022a). However, the chronic use of drugs, such as analgesics and anti-inflammatories, as well as antidepressants used to treat TN, tend to increase the risk of adverse drug reactions. Research in this field has headed towards pain management and pointed out plant-based natural compounds as bases of bioactive molecules that present significant biological properties in this area (Minervini *et al.*, 2022b). Potential therapeutic advantages of natural molecules against several pain-related conditions *in vivo* and *in vitro* were observed in studies that have proven their analgesic, anti-inflammatory and antioxidant effects (Tedesco *et al.*, 2021). Different natural compounds, including carotenoids, polyphenols and polyunsaturated fatty acids, as well as lutein, resveratrol and docosahexaenoic acid ability has appeared to operate through the modulation of both peripheral and central nociceptive neuronal pathways, and anti-inflammatory pathways (Takeda and Shimazu, 2020).

Natural molecules have been raising over the years and they are acknowledged as adjuvants in orofacial pain control and treatment. This finding points out that terpenes are the most prosperous agents in nociception animal models, since they interact through diverse analgesic mechanisms (Rodriguez *et al.*, 2020). These molecules can act in the same systems of opioid drugs by activating descendent inhibitory nociceptive pathways (Corder *et al.*, 2018). According to many reports, terpenes, such as linalool, myrcene, citronellol and citronellal, cause analgesic effects by modulating the opioid system and closing the inflammatory response (Baron, 2018).

Cannabis sativa L. is becoming increasingly relevant to scientific research because its bioactive compounds include terpenes (Lim *et al.*, 2021). The analgesic role of cannabinoids has been observed in several pain conditions, both in animal models and in clinical studies focused on endogenous cannabinoid system modulation in mammalian nociceptive pathways (Tamba *et al.*, 2020). An increasing body of evidence substantiates the potential use of cannabinoid-based formulations to treat chronic inflammation, which can lead to a whole variety of dysfunctions, including orofacial dysfunctions (Grossman *et al.*, 2022; Kopustinskiene *et al.*, 2022). Interestingly, non-psychoactive cannabinoids add to hemp's pharmacological effects. Recently published studies have shown them as promising pain management alternative (Martinez *et al.*, 2020). It is possible hypothesizing that these molecules could be new analgesic agents in orofacial pain conditions if one considers these outcomes and cannabinoids' ability to modulate orofacial nociception pathways (Burgos *et al.*, 2010).

Cannabis Bioactive Compounds

To the best of our knowledge, *Cannabis sativa* L. is one of the most ancient medicinal plants on the globe, and it has called scientists' attention worldwide (Pellati *et al.*, 2018). *Cannabis sativa* L. is an herbaceous plant belonging to family Cannabaceae that carries many secondary metabolites, such as cannabinoids and non-cannabinoid types, in different plant parts (Radwan *et al.*, 2021). Cannabinoids are C21 terpene-phenolic specific in Cannabis, including Δ 9 -tetrahydrocannabinol (THC), which is a psychoactive compound; and cannabidiol (CBD) (Figure 3) which, unlike THC, lacks psychotropic activity, a fact that turns it into an attractive option for medical applications (Mastinu *et al.*, 2021). There is also a group of minor phytocannabinoids, namely: cannabigerol (CBG), cannabidivarin (CBDV), cannabinol (CBN) and cannabichromene (CBC) (Landucci, *et al.*, 2022). The plant produces cannabinoids in their corresponding acid forms, among them one finds Δ 9 - tetrahydrocannabinolic acid (Δ 9 -THCA), which is one of the most abundant cannabinoids in drug-type plants. Fiber-type plants, in their turn, mostly carry cannabigerolic acid (CBGA) and cannabidiolic acid (CBDA) (Pellati,

et al., 2018). Acidic cannabinoids are often decarboxylated to their neutral forms due to external factors, such as light, heat and combustion (Kim *et al.*, 2022).

Cannabis and cannabinoid medicine has been around for centuries (Crescente et al, 2023). A growing number of countries have created a legal framework, according to which, cannabis and its plant extracts are legally accessible. Although, nowadays, it would be great to embrace cannabis as the molecule to revolutionize medicine and improve the lives of millions of Canadians suffering with headaches, orofacial neuropathic pain and temporomandibular joint disease, this scenario is far from real – but, there is significant potential to make it happen. Canada created a legal framework for physicians to authorize medical cannabis in 2013 (NMAR-2013) and it opened room for the Cannabis Act (Bill C-45), which provided on recreational cannabis consumption back in 2018 (Crepault, 2018). It happened after earlier attempts to create a regulated environment guided by physicians, which seemed futile, in the past. The legislation has also approved cannabis for recreational use by adults in 17 U.S. states, yet, 36 U.S. states have medical cannabis policies (NCoS, 2021). Nowadays, cannabis products can be found on almost every street corner, it can be accessed by anyone over 18 years old for recreational purposes. Despite the broader access to cannabis products, and the increased tax revenues due to it, for the time being, it has placed science, and the ability to study cannabis and cannabinoid medicines, on the backburner. Although there is evidence to support cannabis use to treat a whole variety of health-related conditions (NAS-2017), according to recent research published by Health Canada, nearly four million Canadians are self-medicating without a medical document from a healthcare practitioner. It means they are turning to the recreational or illicit market, rather than going through formal medical channels (Canada, 2021). Canadians interested in cannabinoid medicine trials for conditions, such as chronic pain, insomnia and anxiety, often get their cannabis-related medical information form their neighbors, co-workers or from their local "bud-tender". This scenario needs to change for Canadians' safety. Recreational cannabis sales now that exceed 250 million dollars on a monthly basis from the Canadian public (Statista.m 2020; *C*larke, and Kotteeswaran, 2021)

ANVISA (Brazil) approved the Cannabidiol Active Pharmaceutical (20 mg/ml). This measure was published in the Official Gazette (D.O.U), on Monday (4/25), through Resolution RE 1.298/2022 (https://www.gov.br/anvisa/pt-br/assuntos/noticias-anvisa/2022/anvisa-aprova-novo-produto-medicinal-a-base-de-cannabis-1). One of the products is manufactured in Canada and sold in Brazil in solution form. It contains 20 mg/ml cannabidiol (CBD) and no more than 0.2% tetrahydrocannabinol (THC) in its formulation. However, other 15 products were approved by ANVISA in this category, so far, as provided on the Collegiate Board Resolution (RDC) 327/2019. Five of these fifteen products are based on Cannabis sativa extracts and ten of them on phytopharmaceutical cannabidiol.

Using Cannabidiol To Treat Trigeminal Neuralgia (TN)

Neuropathy, or nerve pain, is one of trigeminal neuralgia features. It is caused by nerve damages that can lead to muscle weakness, numbness, pain and tingling sensation. Fiani *et al.*, (2020) have shown that CBD could diminish pain and inflammation resulting from nerve pain. Studies carried out in the last two decades have investigated how CBD - which expressed analgesic properties in both animal models and human clinical trials - helps minimizing pain secondary to TN. It was done to extend the strategy of developing potential alternative medical therapies for TN. Binding CB1R and the subsequently modulation of the descending pathway from the periaqueductal gray (PAG) and rostral ventral medulla in the midbrain, through the spinal cord, is an known mechanism used by CBD to exert its antinociceptive skills (McDonough *et al.*,2014). Animal models have been used to support this finding. The synthetic cannabinoid drug WIN55,212-2 effectively binds CB1R and leads to allodynia inhibition and to hyperalgesia caused by constriction damage of the infraorbital branch of the trigeminal nerve (Chagas *et al.*, 2014). Another preclinical research has pointed out this synthetic cannabinoid's ability to modulate signaling through N-type calcium channels, 5-HT 3 receptor activated ion channels

and GABA receptor ion channels. All these elements have played a role in TN–pain manifestation (McDonough *et al.*, 2014). There is consensus that trials in cannabis-related medical research involving humans are controversial. One trial conducted with 112 patients who smoked cannabis has shown trigeminal neuralgia relief associated with multiple sclerosis (MS) in more than 70% of study participants (Consroe *et al.*, 1997). The cannabis used by patients in this study is different from the traditional CBD, which contains a specific rate of THC - this substance has its own psychotropic and neurologic effects. However, this study emphasized remarkable effectiveness of a cannabis-related substance to relieve TN pain in humans, and it certainly deserves further studies. The diversity of molecular mechanisms used by CBD to produce analgesic effects shines light on its undoubted potential as alternative solution to treat patients suffering from refractory TN (Fiani *et al.*, 2020).

Miost *et al.*, (2020) concluded that CBD could relieve, or curb, pain sensitivity (hyperalgesia). The literature makes it clear that, although most studies on CBD use for TN-treating have been done with animals, it is imperative to run further clinical studies with humans. Mechtler *et al.*, (2019) conducted a study on medical cannabis based on a THC/CBD mix and concluded that it could be effective in pain management in trigeminal neuralgia patients. In total, 81% of the 42 patients included in the study reported improvement in their TN symptoms. Adverse effects were reported by 40% of them - two patients discontinued its use due to adverse effects. The most common side effects comprised fatigue, somnolence, nausea and dizziness. In total, 69% of patients who reported ≥50% improvement in TN symptoms used one product and 50% of patients used 1:1 THC to CBD ratio. In addition, 50% of patients reporting opioid use at the beginning of medical cannabis'(MC) treatment were able to reduce opioid consumption on MC. Based on these results, MC is a useful part of a comprehensive pain management plan developed for TN patients. However, future randomized placebo-controlled trials are needed.

There are few side effects associated with CBD. Most clinical trials did not find mild reactions to CBD. Klumpers& Thacker (2019) mentioned some common side effects, namely: dry mouth, dizziness, drowsiness, fatigue, reduced appetite, nausea, vomiting and diarrhea. Side effects are often mild and they go away after one has gotten used to CBD. CBD is well tolerated in its oil form.

A case report described a 46-year-old man suffering from trigeminal neuralgia for over five years, who presented neuropathic pain in the right suborbital facial region, based on the 10-point Numerical Rating Scale (NRS) (Genovese, *et al.*, 2021). Anamnesis showed no obvious trauma, neither otolaryngological interventions nor odontostomatological issues. Initial treatment recommended carbamazepine (400 mg rp, twice a day) and tapentadol (maximum dose of 300 mg, twice a day). Infraorbital nerve block (both for diagnostic and therapeutic purposes) with 1 ml lidocaine at 1% (10 mg/ml) was performed in association with pharmacological therapy. Initial therapy was not effective in treating pain due to side effects, such as decreased appetite, anxiety, confusion, drowsiness, sleep disturbances and poor pain relief (NRS 8). Therefore, the patient underwent Cannabinoid's therapy (19% THC; <1% CBD), which started with 5 sublingual drops, twice a day, up to 10 sublingual drops, 3 times a day. Pain reduction by 50% (NRS 5) was reported during the pain–assessment follow-up, which started fifteen days after the treatment had begun. Carbamazepine (400 mg rp, once a day) and tapentadol (dose of 100 mg, twice a day) doses were reduced, at this point. After 30 days, the patient did not have to take any opioids, but he continued with the carbamazepine 400 mg rp (once a day) therapy. Ninety days after treatment has started, pain symptoms remained tolerable (NRS 3). The patient reported discomfort and rare "electric shock" sensation during intense stimuli to the face (such as shaving). However, quality of sleep and overall quality of life had improved. The patient experienced modest drowsiness in the first ten days as side effect, but it soon disappeared after adjustments were made in the therapy. The patient continued with the treatment with cannabinoids (19% THC; <1% CBD) 120 days after the start of therapy, namely: 10 sublingual drops, 3 times a day, and carbamazepine 400 mg rp, once a day. This treatment led to good pain relief (NRS 3). Drowsiness, dizziness, blurred vision,

ataxia, headache, nausea and rash are common adverse events observed after concomitant use of Cannabinoids compound and Carbamazepine. However, only a transient side effect was reported by the herein described patient, and it disappeared after therapy adjustments.

A study published in 2004 reported the positive role of cannabinoids in managing trigeminal neuralgia (Liang *et al.*, 2004). Cannabinoid treatment had noticeable effect in the aforementioned publication. The present case reported reduction in NRS values (> 50%) after fifteen days and NRS=3 after 90 days. Treatment based on cannabinoids is safe and causes minimal side effects.

A clinical case report has described the use of nabiximol (CBD 25 mg/mL/THC 27 mg/mL) for 30 days to rule out the trigeminal neuralgia secondary to multiple sclerosis and refractory to other drugs (Gajofatto, 2016). A 54-year-old man with secondary progressive multiple sclerosis (MS) and previous medical history, including left trigeminal neuralgia since the age 49, reported to have undergone multiple pharmacological treatments without any positive outcome or with adverse events. The patient had been previously treated with pregabalin 150 mg, twice a day, for several months and recorded limited benefits for his symptoms, as well as intolerance to higher pregabalin doses (dizziness). Carbamazepin 200 mg, twice a day, was then added to his medical therapy, but it did not lead to significant pain improvement. This therapy was discontinued after 6 months due to excessive somnolence. The patient reported score 8 out of 10 on NRS for spasticity after nabiximols' prescription. The patient was taking nabiximols, 5 sprays a day, and he reported modest improvement in spasticity at the 1-month follow-up (NRS¼6/10). He also observed the recurrence of trigeminal neuralgia episodes and background facial discomfort – which is often felt before treatment –, but these symptoms were fully ruled out after the nabiximols therapy (NRS for pain¼0/10). The benefits and mild side effects of treatment persisted at the 6-month follow-up. Neurological examination was unchanged, but the patient was able to walk independently for less than 100 m. At the 12–month follow-up after nabiximols therapy had started, the patient was clinically stable and reported only few episodes of mild left facial pain, which did not require additional treatment.

Drug Interactions Between Cannabidiol Oil and Commonly Prescribed Drugs for Neuropathic Orofacial Pain (Nop)

Although there is evidence of symptomatic benefits from CBD oil in human populations, anti-inflammatory action triggered by endogenous endocannabinoid system modulation is an interesting addition to CBD oil as feasible analgesics to patients with rheumatic diseases and chronic pain conditions (Barrie and Manolios, 2017).

Studies have shown CBD effect on numerous enzymes up to 2018. According to these studies, CDB could potentially affect how other drugs are metabolized. Reports have shown that CBD can potentially inhibit CYP 1A1 (Yamaori *et al.*, 2010), CYP 2C19 (Bornheim *et al.*, 1993), CYP 2D6 (Yamaori *et al.*, 2011a) and CYP 3A4 (Yamaori *et al.*, 2011b).

Laboratory reports have shown that CBD can suppress the aforementioned enzymes, but several studies carried out with humans did not show consistent results, likely due to the complex extrapolation from preclinical to clinical outcomes.

Many pharmaceuticals are metabolized through CYP enzyme system. However, Gabapentin, which is one of the most useful pain management drugs, is not metabolized through these enzymes.

The exact mechanism used by gabapentin to produce its therapeutic effects is not fully understood, so far. Data in the literature suggests that the primary action mode appears to be at the auxiliary α2δ-1 subunit of voltage-gated calcium channels, although low affinity for the α2δ-2 subunit was also observed. The major role of these subunits lies on favoring the movement of pore-forming α1 subunits of calcium channels from the endoplasmic reticulum to the cell membrane of pre-synaptic neurons. Outcomes have shown that chronic pain conditions can induce increased expression of α2δ subunits and that these changes are correlated to hyperalgesia. Gabapentin appears to inhibit the action of α2δ-1

subunits and, consequently, to decrease pre-synaptic voltage-gated calcium channels' density and to, later on, deliver the excitatory neurotransmitters. Assumingly, this suppression is also responsible for Gabapentin's anti-epileptic action. There is also evidence that Gabapentin acts in both adenosine receptors and voltage-gated potassium channels, although the clinical relevance of its action, at these sites, is unclear (DrugBank, 2023).

Interestingly, Gabapentin is not metabolized to any appreciable degree in humans and it is excreted intact, in the urine. This drug is eliminated from the systemic circulation by renal excretion, as unchanged drug. Its elimination half-life lasts from 5 to 7 hours and it is unaltered by dose or by subsequent multiple dosing (Staiger, 2018).

CBD is not thought to interact with gabapentin due to lack of gabapentin metabolism, and it should not affect gabapentin levels in the body if it is taken at the same time.

The only thing for one to be aware of is that high CBD doses can have sedative and slight hypnotic effects (Carlini and Cunha, 1981). Thus, there is general warning to use CBD cautiously in combination to CNS (central nervous system) depressants, like Gabapentin, given the risks of additive sedation.

A search in the Medicines Information Department at Imperial College Healthcare NHS Trust, and in the British National Formulary, which is a resource maintained by the Therapeutic Research Centre (TRC-2019) (Wilson-Morkeh *et al.*, 2020), showed outcomes linked to important potential drug interactions between CBD oil and common rheumatological medications.

These outcomes made it clear that the drug interaction between CSs and CBD was outstanding. Based on these data, prednisolone and hydrocortisone are metabolized by the cytochrome P450 enzyme CYP3A (Nebert *et al.*, 2013). Cannabidiols, mainly CBD, are powerful CYP3A inhibitors. Therefore, their concomitant use may decrease glucocorticoid clearance and increase the risk of systemic CS side-effects (Yamaori et al, 2011).

Naproxen, which is a non-steroidal anti-inflammatory drug, is another compound broadly prescribed in rheumatology clinic, mainly in recent cares regarding other NSAIDs. Naproxen is metabolized in the liver through CYP2C9, and CBD is classified as direct CYP2C9 inhibitor, because it likely increases the risk of negative actions and accumulation (Yamaori *et al.*, 2012).

Special attention is paid to increased plasma concentration recorded for another commonly prescribed analgesic, namely: pro-drug tramadol. CBD also suppresses the cytochrome P450 enzyme (CYP2D6), and it is paramount for tramadol biotransformation into its active metabolite. Amitriptyline follows a similar behavior, since it is metabolized by the hepatic cytochrome P450, isozymes CYP2D6, CYP1A2, CYP2C19, CYP3A4 and CYP2C9, which are inhibited by CBD. Therefore, there is risk of developing augmented adverse events, such as anticholinergic effects and QT prolongation. Besides these effects, simultaneous CBD use with medicines that exert sedative and anesthetic effects, such as Gabapentin and Pregabalin, may potentially cause additive therapeutic and adverse effects. However, significant outcomes from Gabapentin using showed no interaction with hepatic enzymes, since over 95% of it is eliminated through renal excretion. Other antidepressants, which are prescribed for rheumatic disease, such as Sertraline, Citalopram, Paroxetine and Mirtazapine are all followed by the metabolism of cytochrome enzymes that, in their turn, have seemed to be inhibited by CBD.

It is essential mentioning that Janus kinase inhibitors used in autoimmune inflammatory arthritis diverge in their interaction side views. Tofacitinib, for example, is mainly metabolized in the liver by CYP3A4 and CYP2C19 - these two isoenzymes are inhibited by CBD. Their simultaneous use could likely lead to increased serum levels and unpleasant effects. On the other hand, Baricitinib is exclusively cleared by the kidneys and it has extremely low mediation by CYP3A4, which leads to positive profile without significant predicted interactions with CBD.

It is important noticing that Wilson-Morkeh *et al.*, (2020) did not find any predictable interactions with most Disease-modifying antirheumatic drugs (DMARDs) or biologics, such as

Methotrexate (MTX), Hydroxychloroquin (HCQ), Sulfasalazine (SSZ), Mycophenolate mofetil (MMF), Mesalazine, Adalimumab, Etanercept, Abatacept, Infliximab or Rituximab. Similarly, no significant interactions were anticipated with IL-1 or IL-6 receptor antagonists.

This excellent review pointed out the importance of taking comprehensive drug histories by asking about drugs considered alternative medicines and food supplements (Wilson-Morkeh *et al.* 2020).

No investigations in the literature found higher Pregabalin levels in the brain after the use of lycoprotein P (Pgp) inhibitors (Schifano, 2014). The potential pharmacokinetic interactions among CBD and antiseizure drugs were discussed (Table 1) (Lile *et al.*, 2016).

Table 1: *Gabapentin and antiseizure medication interactions with cannabidiol (modified from Almuntashiri et al., 2022).*

Type of study	Antiseizure medication (ASM)	Pharmacodynamic interaction	Pharmacokinetic effect of Cannabidiol (CBD) on ASM	Pharmacokinetic effect of ASM on CBD	Effect of interaction	Possible mechanism
Pre-clinical	Gabapentin	Cannabidiol (CBD) increases the activity of gabapentin (may however be due to pharmacokinetic interactions).	Increase serum & brain levels of gabapentin with CBD.	No effect of gabapentin with CBD.	Cannabidiol (CBD)increase the activity of gabapentin.	Unclear - may be attributed to penetration in brain or elimination through kidney (gabapentin is not attached with plasma proteins or metabolized by cytochrome P450s, & eliminated as unchanged drug).

Pre-clinical investigations have suggested that gabapentin regulates the corticotropin-releasing factor (CRF)-associated activation of GABA in the brain. This activation is related to increased chances of alcohol dependence and, consequently, to cannabis use. The grounds withdrawal from cannabis, like alcohol withdrawal, cause both anxiogenic-like state and greater extrahypothalamic CRF release in the central part of the amygdala, in animals. The GABA/CRF interaction, and the part they play in the persuasive aspects of abuse relapse, give a compelling pre-clinical reasoning for the investigation on Gabapentin efficacy in cannabis dependency. Besides, based on the clinical investigations of different ailments, Gabapentin has been shown to lessen desires, and mood and sleep disturbances, which are among the most relentless effects of extended cannabis withdrawal and the main cause of patients' continuous cannabis use.

Gabapentin also showed subtle cognitive improvement in concentration, attention, visual-motor activities, inhibition, among others, in healthy individuals. Consequently, gabapentin reestablishes homeostasis in the normal brain stress system (CRF) through calcium channel-GABAergic mechanistic action. It may provide a new management tactic that can be compared to agonistic, antagonistic, or psychiatric medications that have been investigated to date for managing cannabis dependency. A previous study with 50 people looking for treatment against cannabis dependency was based on giving 1,200 mg/day of Gabapentin in an 84-day double-blind, randomized, placebo-controlled efficacy trial. Treatment with Gabapentin reduced cannabinoid (CB) metabolite levels in urine, in self-reported score on use cannabis' craving, supported by questionnaires about depression. It has further enhanced the performance in executive function tests in comparison to placebo controls. If one takes into

consideration these positive results and lack of presently approved drugs for cannabis abuse, the investigation of mechanistic pathways taken by Gabapentin to act as strong pharmacotherapeutic is expected to encourage future drug development endeavors. Cannabis constituents interact with several antiseizure medications at pharmacokinetic and pharmacodynamic levels. Pharmacokinetic interactions between cannabis constituents and gabapentinoids have been reported. However, not all these interactions affect the therapeutic action, but, yet further clinical studies are needed to determine how these drug interactions influence clinical practices (Almuntashiri *et al.*, 2022).

Declarations

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Author contributions

ND, CAAC: Formal analysis, Investigation, Methodology, Supervision, Validation, Visualization, Writing - original draft. MSD: Data, collection and analyses. ND, MSM, WJF, CAAC: Formal analysis, supervision of manuscript. Final editing manuscript.

Competing Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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