Monográfico

The therapeutic use of cannabis and cannabinoids

El uso terapéutico del cannabis y los cannabinoides

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Abstract

Cannabinoids mainly target the endocannabinoid system, which emerges as a potentially interesting therapeutical target due to its major role in modulating key biological processes throughout the body. As such, cannabinoids have already been proposed as, for example, anti-emetics, anti-spasticity agents, appetite stimulants, anti-epileptic, analgesic, depressants of intraocular pressure or as agents to control movement disorders in Tourette syndrome.

Here, we reviewed the research evidence available regarding the use of cannabis and cannabinoids for a set of suggested therapeutical applications, and addressed some of the short- and long-term risks that have been correlated with the use of these substances.

We found scarce scientific evidence supporting the use of cannabis-based products for most of the suggested applications, as well as no unmet medical need that is not already tackled by existing medicines (some cannabinoid-based) in the market. In such a scenario, the potential risks associated with the chronic use of these substances may deter their medical use.

Keywords

Endocannabinoid system; Cannabidiol; Medical cannabis; Nabiximols; Δ^9-Tetrahydrocannabinol (THC)

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Resumen

Los cannabinoides se dirigen principalmente al sistema endocannabinoide (ECS), que surge como un objetivo terapéutico potencialmente interesante debido a su importante papel en la modulación de procesos biológicos clave en todo el organismo. Como tal, los cannabinoides ya se han propuesto como, por ejemplo, antieméticos, agentes antiespásticos, estimulantes del apetito, antiepilépticos, analgésicos, depresores de la presión intraocular o como agentes para controlar los trastornos del movimiento en el síndrome de Tourette.

Aquí revisamos las pruebas de investigación disponibles sobre el uso del cannabis y los cannabinoides para un conjunto de aplicaciones terapéuticas sugeridas, y abordamos algunos de los riesgos a corto y largo plazo que se han correlacionado con el uso de estas sustancias.

Encontramos escasas pruebas científicas que apoyen el uso de productos basados en el cannabis para la mayoría de las aplicaciones sugeridas, así como ninguna necesidad médica no satisfecha que no esté ya abordada por los medicamentos existentes (algunos basados en cannabinoides) en el mercado. En este escenario, los riesgos potenciales asociados al uso crónico de estas sustancias pueden disuadir su uso médico.

Palabras clave

Sistema endocannabinoide; Cannabidiol; Cannabis medicinal; Nabiximoles; Δ^9-Tetrahidrocannabinol (THC).

1. INTRODUCTION

About 192 million people have been estimated to have used cannabis in 2018, making it the most used psychoactive substance worldwide, according to the 2021 World Drug Report (UNODC, 2021). D^9-Tetrahydrocannabinol (THC) and cannabidiol (CBD) are the main cannabinoids found in cannabis. THC represents its main psychoactive element, whereas CBD is a negative allosteric modulator of the cannabinoid type-1 receptor that antagonizes some of THC's effects and does not elicit psychoactive effects (Cristino et al., 2020).

The new psychoactive substances (NPS) market has also witnessed regular cannabis users searching for more potent cannabinoids turning into synthetic cannabinoids (SCs). SCs comprise a chemically diverse group of substances that mimic the effects of THC, although with higher potency and duration. Of note, these substances dominated the NPS market between 2009 and 2019, but the number of new SCs reaching the market per year has decreased during 2014-2018 (UNODC, 2021). Also, the toxicity of these SCs is often unpredictable and poorly understood, having been increasingly associated with intoxications and deaths, compared to cannabis, which embodies a major challenge for public health and policy-makers (EMCDDA, 2020).

Over the past years, products based on phyto- and synthetic cannabinoids have been explored for distinct therapeutical applications. For example, dronabinol and nabilone (synthetic analogs of THC, sold under the brands Marinol® and Cesamet®, respectively) have been used in clinical settings to attenuate nausea and vomiting in cancer patients undergoing chemotherapy or as adjunct analgesics to alleviate chronic pain (Davis, 2008; de Vries et al., 2014). At the same time, there seems to be a reduced public perception of the risks associated with cannabis and cannabinoids, which according to the most recent World Drug Report, has contributed to their increased non-medical use over the past years, especially by adolescents and young adults, seeking psychotropic effects like relaxation, elevated well-being sensation, or social disinhibition. Although the potency of cannabis products is known to have quadrupled over the past 25 years, the percentage of adolescents that perceive it as harmful has dropped around 40% during that same period (UNODC, 2021).

Recently, self-isolation related to the Covid-19 pandemic has been reported to aggravate cannabis use among its users in about 20% (Bartel et al., 2020). Moreover, recent changes in cannabis and its derivatives' legal status may increase their recreational and medical use (Hall et al., 2019), thus becoming of utmost importance to understand the balance between the risks and benefits of the therapeutical use of cannabinoids.

Here, we analyze the research evidence underlying some of the therapeutical applications of cannabis and cannabinoids under public discussion, and examine the risks of the medical use of these substances.

2. THE ENDOCANNABINOID SYSTEM: A KEY MODULATOR OF BIOLOGICAL FUNCTION

The endocannabinoid system is a complex signaling network composed of endogenous cannabinoids (e.g., anandamide, 2-arachidonoylglycerol), endocannabinoid-like mediators (e.g., long-chain N-acyl amides), enzymes involved in endocannabinoid synthesis (e.g., diacylglycerol lipase alpha, N-acylphosphatidylethanolamine (NAPE)-specific phospholipase D) and degradation (e.g., monoacylglycerol lipase, fatty acid amide hydrolase), cannabinoid receptors (e.g., CB1, CB2) and other cannabinoid targets, including peroxisome proliferator-activated receptor-α (PPARα), G protein-coupled receptor 18 (GPR18), 55 (GPR55) and 119 (GPR119), and the transient receptor potential vanilloid 1 channel (TRPV1) (Alexandre et al., 2019; Mechoulam et al., 2014). Endocannabinoid signaling overlaps with several other pathways and alternative metabolic processes, affecting a larger endocannabinoid-related network generally designated as the endocannabinoidome, which is known to regulate several biological functions (e.g., neurotransmitter release, immune function, pain modulation, vasodilation-mediated thermoregulation, energy metabolism) (Cristino et al., 2020).

All three types of cannabinoids (i.e., endo-, phyto- and synthetic) modulate the endocannabinoid system mainly by binding and activating the classical cannabinoid receptors (CBRs), type-1 (CB1) and type-2 (CB2). Both CB1 and CB2, which belong to the G protein-coupled receptor (GPCR) family, are able to inhibit adenylate cyclase and cyclic adenosine monophosphate (cAMP) pathways, although only the CB1 has been shown

to modulate calcium and potassium channels. Of note, CB1 and CB2 are not exclusively present in a specific type of cells or tissues, rather being widely distributed, at different densities, throughout various organs and tissues (Pertwee et al., 2010). CB1 activation is mostly associated with the psychoactive effects of cannabinoids, with these receptors being mainly prevalent in the pre-synaptic terminals of neurons from the hippocampus and prefrontal cortex, although they can be present at a lower density in basal ganglia and post-synaptic areas (e.g., neurons, glia cells, endothelial brain cells). CB2 receptors are found at a higher density in cells from the immune system (e.g., B-lymphocytes, mast cells, macrophages), thus playing a key role in immune modulation. Nevertheless, CB2 may be also found in the brain, mainly in microglia and at post-synaptic terminals of neurons, as well as in other peripheral tissues (e.g., spleen, tonsils, liver, lung, kidney, gastrointestinal tract) (Howlett and Abood, 2017). Interestingly, up-regulation of CB2 has been observed in some pathological conditions (e.g., anxiety, inflammation, epilepsy, addiction), suggesting its involvement in neuropsychiatric disorders (Chen et al., 2017).

Given the plethora of biological processes in which the endocannabinoid system is involved and the multiplicity of targets that compose the endocannabinoidome, endocannabinoid signaling arises as an appealing therapeutic target.

3. LEGISLATION ON MEDICINAL USE OF CANNABIS AND CANNABINOIDS

Cannabis is considered an illicit drug among countries that signed the 1961 United Nations Single Convention on Narcotic Drugs, but the use of cannabis or cannabis-based products as a medicine to treat defined therapeutic indications is not prevented by this Convention (EMCDDA, 2018). Since the 1960s, more permissive changes to laws regarding the medical and non-medical use of cannabis have been discussed, based on the perceived reduced harms of cannabis use, compared to other psychoactive drugs (Room et al., 2010). This debate has been renewed in the last decade, as some US states and Uruguay legalized the supply and use of cannabis for recreational purposes in 2012. However, proposals to legalize cannabis has raised concerns among policy-makers from other countries that it may result in higher cannabis use, with an increase in its associated harms (EMCDDA, 2018).

In 1996, the state of California (USA) approved the use of cannabis to treat nausea, weight loss, pain, muscle spasm, and serious medical conditions (Conboy, 2000). This approval was followed by more than 30 US states, although with variations regarding, for example, the qualifying medical conditions, the type of cannabis-based product allowed, or the amount of THC and CBD present (Leung et al., 2018). In 2001, Canada allowed the use of cannabis for medicinal use under exceptional circumstances, and since 2014, patients are allowed to buy cannabis from licensed producers following medical recommendations (Ablin et al., 2016).

Cannabinoids (e.g., dronabinol, nabiximols) medically approved by European regulatory agencies can be used in some European countries (Hall et al., 2019). However, there is no harmonized law in the European Union (EU) regarding cannabis use, being each EU member state responsible for the criminal and administrative response to such use. For example, countries like Croatia, Portugal, Luxembourg, and Slovenia have

decriminalized cannabis use and personal possession (still, drugs can be confiscated and non-criminal penalties may be applied). Other countries, including Austria, Germany, and Poland have depenalized cannabis use (EMCDDA, 2018). In the EU, only the Netherlands allows the medicinal use of the cannabis flower. In Israel, doctors may prescribe cannabis for medical use in situations where recognized treatments have failed (Ablin et al., 2016). In 2019, Portugal also adopted similar legislation, allowing the prescription of cannabis-based products in cases where classical treatments with authorized medicines do not produce the desired effects or cause relevant adverse events (Ministry of Health of the Portuguese Republic, 2019). The same decree-law further defines that the activities concerning cannabis-based products for medicinal use (e.g., cultivation, production, commercialization, and import/export) require authorization from the National Authority of Medicines and Health Products (INFARMED, I.P.).

4. PROPOSED THERAPEUTICAL APPLICATIONS OF CANNABIS AND CANNABINOIDS

Cannabis and cannabinoids use has been proposed to treat a few pathological conditions (e.g., multiple sclerosis-associated spasticity, nausea and vomiting). Below we discuss the research evidence supporting such applications, as well as the suitability of using cannabis-based products as an alternative therapeutic in such cases. Table I summarizes the clinical evidence and the evidence level for each case.

4.1. Spasticity associated with multiple sclerosis or spinal cord lesions

Multiple sclerosis (MS) is a potentially disabling auto-immune disorder of the central nervous system (CNS), in which the immune system causes the destruction of myelin, the protective sheath of nerve fibers in the brain and spinal cord (Gao et al., 2018). Among the several symptoms associated with MS (e.g., cognitive disability, sensory alterations, pain), spasticity is one of the most frequent. MS-related lesions in the nerves of the brain and spinal cord causes an interruption of the electric signal communication derived from these areas (Fernández, 2014; Fernández et al., 2020). The inhibitory influence of the corticospinal tract is essential to control the balance of the stretch reflex arc that helps maintain muscle tone (Mukherjee and Chakravarty, 2010). Loss of this inhibition due to corticospinal injury may thus induce hyperexcitable segmental spinal reflex arcs in the alpha motor neurons, leading to the spasticity-characteristic dysregulation of muscle tone control (Centonze, 2014).

Dysfunctional glutamatergic excitation and/or gamma-aminobutyric acid(GABA) ergic inhibition particularly seem to play a major role in MS (Gao et al., 2018). For example, Mandolesi et al. (2015) reported the enhancement of glutamatergic transmission in a mouse model of MS, which was associated with a reduced expression and activity of the excitatory amino acid transporter 1 (EAAT1). In another study, glutamate was found to decrease in white matter over time in patients with the secondary progressive form of the disease (MacMillan et al., 2016). Several clinical studies have also noted alterations in GABA levels in MS patients. For example, higher GABA levels were reported in sensorimotor regions in relapsing-remitting MS compared to healthy controls (Nantes et

al., 2017). However, other studies reported lower GABA levels in sensorimotor regions and in the hippocampus of patients with secondary progressive MS (Cawley et al., 2015).

Presently, there is no cure for MS or MS-associated spasticity, although current management therapies may help slow down the progression of the disease (Fernández et al., 2020).

Due to their ability to reduce glutamate excitotoxicity (Rodríguez-Muñoz et al., 2016), exogenous cannabinoids arise as an alternative to reduce nerve loss in MS patients. Interestingly, there is moderate evidence that nabiximols (a standardized combination of equal amounts of THC and CBD) may be used in the treatment of MS-related spasticity. For example, small improvements in spasticity were observed in MS patients given nabiximols, compared to placebo (total of 6 randomized clinical trials), although no statistical significance was observed in most studies (Whiting et al., 2015). Other studies have reported improvements in symptoms related to spasticity, like incontinence, or pain, rather than spasticity itself (Fernández et al., 2020).

In this sense, it seems reasonable that MS patients are primarily treated with conventional therapies and that nabiximols may only be used in cases that do not respond to such standard therapies. Notably, there is already a commercially available medicine, approved by regulatory agencies (e.g., FDA), with nabiximols (Sativex®, a spray containing 2.7 mg THC and 2.5 mg CBD). Most important, as Sativex® has just completed (in 2021) 10 years under commercialization, pharma companies may submit authorization requests to market their own Sativex-related generic medicines. In this sense, the use of cannabis-based products to treat MS-associated spasticity seems unnecessary and possibly counter-productive.

4.2. Nausea and vomiting in patients undergoing chemo- or radiotherapy, with HIV or hepatitis C

Chemotherapeutic drugs may cause nausea and vomiting as a result of their activation of neurotransmitter receptors present in the brain's area postrema or in the terminal ends of the vagal afferents near the enterochromaffin cells in the intestine. These afferent fibers send the stimuli to the brainstem, which then processes the emetic reflex and triggers efferent signals to other organs that stimulate vomiting (Navari and Aapro, 2016).

Cannabinoids may display an anti-emetic activity by activating CB1 and 5-hydroxytryptamine 3 (5-HT_3) receptors in the dorsal vagal complex (DVC), which regulates emesis, especially the area postrema. Specifically, studies in animal models have shown that cannabinoids may control emesis, either allosterically inhibiting 5-HT_3 receptors in the DVC, or by activating presynaptic CB1 receptors, which subsequently results in a decrease of serotonin release into the synapse (Taylor et al., 2021).

Moreover, serotonin release from enterochromaffin cells in the gastrointestinal tract activates serotonergic receptors on vagal primary afferent nerves. In turn, these afferent nerves transmit the stimuli to the brain, which processes the emetic reflex and signals organs and tissues to induce vomiting. Activation of CB1 in enterochromaffin cells by a CB1 receptor agonist may thus reduce serotonin release from these cells, blocking the emetic signaling (Sharkey et al., 2014).

An analysis of 28 clinical trials assessing the efficacy of cannabinoids to treat nausea and vomiting due to chemotherapy showed no statistically significant effect of cannabinoids compared to active comparators (e.g., prochlorperazine, chlorpromazine, domperidone) or placebo. However, the average number of patients showing complete nausea and vomiting response was higher in those individuals treated with cannabinoids (dronabinol or nabiximols) compared to placebo (Whiting et al., 2015).

In the US and Canada, dronabinol (Marinol® capsules and Syndros® oral solution) and nabilone (Cesamet®) have been approved by the FDA for the treatment of chemotherapy-induced nausea and vomiting, in cases where first-line anti-emetics fail (Warr and Hesketh, 2020). It is worth noting that these medicines are only recommended for adults, as their safety and efficacy have not been established for patients under 18 years old, mostly due to their psychoactive effects. Moreover, there are scarce trials comparing these treatments with newer anti-emetic drugs (Whiting et al., 2015). Studies on murine models have suggested that CBD is able to control emesis by reducing serotonin release through the indirect activation of 5-HT_{1A} receptors, at a limited dose range. However, the authors further concluded that CBD is less effective than THC in reducing nausea and vomiting (Parker et al., 2011; Russo et al., 2005).

In patients with the human immunodeficiency virus (HIV), cannabinoids were shown to increase weight and appetite but failed to reduce nausea and vomiting (Mücke et al., 2018b). Also, the use of cannabis-based products in the treatment of nausea and vomiting resulting from medication for hepatitis C is scarce and has not shown any statistical significance (Costiniuk et al., 2008).

4.3. Appetite stimulation in patients in palliative care (e.g., cancer, HIV)

The hyperphagic action of THC has been shown to be mediated by CB1 receptors (Kirkham, 2009). THC increases the activity of 5'-adenosine monophosphate-activated protein kinase (AMPK) in the hypothalamus (while inhibiting its activity in the liver and adipose tissue). In turn, this enzyme phosphorylates acetyl CoA carboxylase, thus inhibiting the fatty acid synthesis and promoting their oxidation. Fatty acid oxidation further results in a reduction in the storage of lipids, which in turn stimulates appetite (Kola et al., 2005). To the best of our knowledge, there is scarce evidence that cannabinoids are better than placebo in improving appetite in cancer patients under palliative care (Mücke et al., 2018a).

There is also weak evidence supporting the stimulation of appetite by synthetic THC in individuals with HIV/AIDS. In four clinical studies assessing dronabinol-induced appetite stimulation in HIV/AIDS patients, three were compared with placebo and one with megestrol acetate. Dronabinol promoted an increase in body weight and showed limited evidence of its ability to increase appetite, compared with placebo. However, no statistical significance was found for such an association. Also, these effects were less evident compared with megestrol acetate (Abrams, 2018; Whiting et al., 2015).

4.4. Chronic pain

Cannabinoids have been suggested to have an antinociceptive action mostly through the activation of TRPV1 or the metabotropic GPR18 and GPR55 receptors. The TRPV1 is a non-selective cationic channel exogenously activated by high tem-

peratures or capsaicin, for example. It acts as a molecular integrator of chemical and noxious heat stimuli responses, modulating nociceptive responses. Activation of TRPV1 channels in the sensory neurons, where they are highly expressed, triggers calcium influx, neurotransmitter release, and the transmission of pain or noxious stimuli (Marrone et al., 2017). Partial activation of these ionotropic receptors may fail to reach the threshold levels required to excite nociceptors. As a result, the depolarization of membrane potential of nociceptors may cause the inactivation of voltage-dependent ion channels, like TRPV1 (Bennett et al., 2019). The orphan receptors GPR18 and GPR55, which are also targeted by cannabinoids, are expressed in the central and peripheral nociceptive systems, seemingly playing a key role in sensory transmission and pain integration, and having already been proposed to be involved in the modulation of acute and chronic pain (Guerrero-Alba et al., 2019).

Data regarding the analgesic potential of cannabinoids remains equivocal. For example, a recent study suggested cannabis as a potential therapy for fibromyalgia, a disease characterized by chronic widespread pain (Berger et al., 2020). In a double-blind, randomized, placebo-controlled clinical trial conducted during eight weeks to assess the effects of THC-rich cannabis oil on fibromyalgia, the authors observed no significant differences in baseline Fibromyalgia Impact Questionnaire (FIQ) score between cannabis-treated and placebo groups. However, the analysis of isolated FIQ items displayed significant improvement of "feel good", "pain", "do work" and "fatigue" scores in the cannabis group compared with placebo, whereas the placebo significantly ameliorated the "depression" score after intervention (Chaves et al., 2020).

A recent meta-analysis examined the data from 28 clinical trials evaluating the action of nabiximols, nabilone, dronabinol, THC oromucosal spray, smoked THC, or vaporized cannabis on different conditions causing chronic pain (e.g., neuropathic, cancer, diabetic neuropathy, fibromyalgia). In general, cannabinoids seemed to improve the scores of pain-related parameters, compared to placebo, although in most cases data failed to attain statistical significance (Whiting et al., 2015).

4.5. Movement disorders in Gilles de la Tourette syndrome

Only two small placebo-controlled clinical trials have evaluated the potential of cannabinoids, namely THC oral capsules, to improve tic severity in patients with Tourette syndrome (Muller-Vahl et al., 2002; Muller-Vahl et al., 2003). The authors observed a significant improvement of tic severity in THC-treated patients, compared to placebo. However, this tic severity only decreased less than one point in a scale ranging between 0 and 6. In addition, the trials were reported to have great bias risk (Abrams, 2018). There is a clinical trial ongoing to assess the efficacy and safety of nabiximols in the treatment of chronic tic disorders (Jakubovski et al., 2020). It thus seems reasonable to allow this clinical trial to come to an end before ascertaining the suitability of cannabinoids for this therapeutical indication.

4.6. Epilepsy and other convulsion-associated disorders (e.g., Dravet and Lennox-Gastaut syndromes)

CBD has been reported to exert an overall inhibitory effect on sodium and calcium channels, which modulates the membrane

electrical potential and subsequently reduces neuronal hyperactivity, suggesting its potential use in the treatment of epilepsy. Such an effect may be achieved through the desensitization of the TRPV1 channels, or by acting as an antagonist at GPR55 receptors. CBD may further block the transport of nucleotides by equilibrative nucleotide transporter (ENT)1, which reduces adenosine uptake and leads to the accumulation of adenosine in the extracellular medium (de Almeida and Devi, 2020).

A systematic review of the potential of cannabinoids to treat epilepsy found no high-quality randomized trials, concluding that there was not enough data to either support or rebut the use of cannabinoids in epilepsy (Koppel et al., 2014). Nevertheless, the use of cannabis-based products to treat convulsion-associated disorders seems unnecessary, as there is an already an approved and marketed CBD-based medicine, Epidiolex®, which has been reported to reduce the frequency of epileptic seizures in children (> 2-year-old) with Dravet and Lennox-Gastaut syndromes, when added to other antiepileptic drugs (Sekar and Pack, 2019).

4.7. Therapy-resistant glaucoma

Glaucoma has been frequently suggested as a potential indication for the medical use of cannabis and cannabinoids, mostly based on early findings that cannabis could reduce intraocular pressure, which is one of the main contributors to this disorder (Green, 1979). However, distinct ophthalmological societies do not recommend cannabis for glaucoma treatment. For example, based on reviews from the National Eye Institute, the Institute of Medicine, and the evidence available, the Complementary Therapy Task Force of the American Academy of Ophthalmology found no scientific evidence demonstrating a higher benefit and/or risk reduction of using cannabis in the treatment of glaucoma, compared with conventional therapies. In particular, the cannabinoid action is short-lived, is often associated with the development of tolerance, and there is a high incidence of undesirable psychotropic effects and other adverse events (Complementary Therapy Task Force of the American Academy of Ophthalmology, 2014). This recommendation is supported by the American Glaucoma Society and by the Canadian Ophthalmological Society.

Of note, a small pilot study comprising only 6 participants, with an unclear risk of bias, found no differences between cannabinoids (e.g., THC, CBD) on measures of intraocular pressure in patients with glaucoma (Tomida et al., 2006).

Table 1. Clinical trial evidence for the use of cannabis and cannabinoids for the treatment of distinct pathological conditions

Pathology	Trials	Main Findings	Evidence level	References
Spasticity associated with Multiple Sclerosis	11 studies including patients with MS treated with nabiximols (6), dronabinol (3), nabilone (1), THC/CBD (4, 2 of which also including dronabinol), ECP002A (1) and smoked THC (1). All studies were placebo-controlled. Risk bias was low for 2 studies, high for 7 and unclear for 5.	Non-statistically significant improvements in spasticity were observed in MS patients given nabiximols, compared to placebo	Moderate	(Whiting et al., 2015)
	Observational studies conducted in three European countries (e.g., UK, Spain, Germany) assessing the effects of daily THC:CBD oromucosal spray on MS patients.	Improvements in symptoms related with spasticity (e.g., incontinence, pain), rather than spasticity itself		(Fernández, 2014)
Nausea and vomiting	28 clinical trials: 14 assessing the effects of nabilone, 3 for dronabinol, 1 for nabiximols, 4 for levonandatrol, 6 for THC. 2 studies included a combination therapy of dronabinol plus ondansetron or prochlorperazine. 8 studies were compared to a placebo, 3 of which also included an active comparator. 20 studies only included an active comparator: prochlorperazine (15 studies), chlorpromazine (2 studies) or domperidone (2 studies). Risk bias was high for 23 studies and unclear for 5.	In all studies, no statistical significance was found between the effects of cannabinoids and active comparators or placebo. The average number of patients showing a complete nausea and vomiting response was higher in those treated with cannabinoids (dronabinol or nabiximols) compared to placebo. In the US and Canada, dronabinol and nabilone have been approved by the FDA to treat chemotherapy-induced nausea and vomiting, in cases where first-line anti-emetics fail.	Low-Moderate	(Warr and Hesketh, 2020; Whiting et al., 2015)
	Meta-analysis of 4 double-blind or open label randomized controlled trials with parallel or crossover design and a duration of ≥ 2 weeks and ≥ 10 patients per study arm. HIV/AIDS patients were administered dronabinol: 3 studies compared with placebo and 1 with megestrol acetate. All 4 trials had a moderate risk of bias.	Cannabinoids failed to reduce nausea and vomiting in patients with the HIV/AIDS patients.	Low	(Mücke et al., 2018b)
	25 out of 191 hepatitis C patients (13%) undergoing interferon-ribavirin therapy were initiated with oral cannabinoid therapy.	The use of cannabis-based products in the treatment of nausea and vomiting resulting from medication for hepatitis C is scarce and has not shown any statistical significance	Low	(Costiniuk et al., 2008)

(Table continues on next page)

Pathology	Trials	Main Findings	Evidence level	References
Appetite stimulation in palliative care patients	4 clinical studies in which HIV/AIDS patients were administered dronabinol: 3 studies compared with placebo and 1 with megestrol acetate.	Dronabinol promoted an increase in body weight, but showed limited evidence (no statistical significance) of increasing appetite, compared with placebo. These effects were less evident compared with megestrol acetate.	Low	(Abrams, 2018)
Chronic pain	Double-blind, randomized, placebo-controlled clinical trial conducted during eight weeks to assess the effects of a THC-rich cannabis oil on fibromyalgia	There were no significant differences on baseline Fibromyalgia Impact Questionnaire (FIQ) score between cannabis-treated and placebo groups. The analysis of isolated FIQ items displayed significant improvement of "feel good", "pain", "do work" and "fatigue" scores in the cannabis group compared with placebo, whereas the placebo significantly ameliorated the "depression" score.	Low-Moderate	(Chaves et al., 2020).
	28 studies, evaluating the effects of nabiximols (13), THC (4), nabilone (5), THC oromucosal spray (3), dronabinol (2), vaporized cannabis (1), ajuvenic acid capsules (1), and oral THC (1). All studies were compared to placebo, except one that compared nabilone with amitriptyline. Risk bias was low for 2 studies unclear for 9, and high for 17.	Cannabinoids generally seemed to improve the scores of pain-related parameters, compared to placebo, but in most cases failed to reach statistical significance	Low	(Whiting et al., 2015)
Tourette syndrome	2 small placebo-controlled clinical trials have evaluated the potential of cannabinoids, namely THC oral capsules, to improve tic severity in patients with Tourette syndrome. Risk bias was high for both studies.	Tic severity was only slightly (although significantly) improved in THC-treated patients, compared to placebo.	Low	(Muller-Vahl et al., 2002; Muller-Vahl et al., 2003)
	Ongoing clinical trial to assess the efficacy and safety of nabiximols in the treatment of chronic tic disorders	No available data so far.	---	(Jakubovski et al., 2020).
Epilepsy and convulsion-associated disorders		There are no high-quality randomized clinical trials that have assessed the effects of cannabinoid use on epilepsy.	Low	(Koppel et al., 2014)
		There is an approved CBD-based medicine, Epidiolex®, in the market. Epidiolex was reported to reduce the frequency of epileptic seizures in children with Dravet and Lennox-Gastaut syndromes, when added to other anti-epileptic drugs.	Moderate	(Sekar and Pack, 2019)

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Pathology	Trials	Main Findings	Evidence level	References
Glaucoma		The American Academy of Ophthalmology, the American Glaucoma Society and the Canadian Ophthalmological Society do not recommend the use of cannabis or cannabinoids to treat glaucoma.	None-very low	(Complementary Therapy Task Force of the American Academy of Ophthalmology, 2014)
	Small pilot study comprising only 6 participants. Risk bias was unclear.	No significant differences were found between cannabinoids (e.g., THC, CBD) on measures of intraocular pressure in patients with glaucoma.		(Tomida et al., 2006)

5. RISKS ASSOCIATED WITH CANNABIS AND CANNABINOIDS

Cannabinoid use has been correlated with a plethora of acute and chronic adverse effects at the neurological (e.g., impaired cognition and motor coordination, hallucinations, paranoia), cardiovascular (e.g., tachycardia, chest pain, stroke), respiratory (e.g., respiratory depression), renal (e.g., acute kidney injury), or gastrointestinal (e.g., nausea, vomiting) systems (Cohen and Weinstein, 2018; Pasman et al., 2018). In particular, the risks of cannabinoid use to mental health, namely the association of cannabinoid use with the onset of psychotic disorders, has been debated over the last decades. A recent study showed that cannabis doubled the risk of inducing psychotic disorders in vulnerable individuals (Ortiz-Medina et al., 2018). Moreover, a recent clinical trial concluded that daily cannabis users had a 3.2-fold higher risk of developing neuropsychiatric disorders compared to individuals that had never used cannabis (Di Forti et al., 2019). Most accepted mechanisms underlying this association include: a genetic susceptibility to cannabinoid-induced psychosis, as several studies have observed that cannabinoids affect the expression of genes commonly found dysregulated in psychotic disorders (Guennewig et al., 2018; Morgan et al., 2016); the cannabinoid-mediated disruption of major neurotransmitter (e.g., dopamine, glutamate, GABA, serotonin) signaling (Modinos et al., 2018; Zou and Kumar, 2018); and the dysregulation of neurogenesis (Alexandre et al., 2019; Renard et al., 2018). Of note, the impact of cannabinoid use on neurodevelopment represents a core issue, considering that adolescents and young adults (including pregnant women/women of childbearing age) are among the most common cannabinoid users and that the developing brain is especially vulnerable to cannabinoid-elicited effects, due to the key role played by the ECS in neurogenesis regulation (Alexandre et al., 2019; Malheiro et al., 2021).

Prenatal and adolescent cannabis and cannabinoids use have also been reported to promote epigenetic changes, like DNA methylations or histone modifications, which may also ultimately impair neurogenesis (Gomes et al., 2020; Szutorisz and Hurd, 2018). For example, exposure of adolescent female rats to THC induced histone modifi-

cations with an impact on the expression of genes related to synaptic plasticity that play a key role in cognitive function (Gomes et al., 2020; Szutorisz and Hurd, 2016). Interestingly, it has been shown that the offspring of animals administered cannabinoids develop a drug-seeking behavior during adulthood (DiNieri et al., 2011). Moreover, these substances have also been reported to induce a series of neurobiological changes consistent with the development of cannabis use disorder, which in most cases assumes the form of addiction (Hasin et al., 2015; Zehra et al., 2018).

6. CONCLUSIONS

The debate over the potential therapeutical applications of cannabis and cannabinoids has resurfaced in recent years, mostly due to the recent changes in their legal status in some countries. However, as we demonstrated, there is still scarce scientific evidence supporting most of such applications, and in the cases where there is enough evidence, there are already approved cannabinoid-based (e.g., nabiximols or CBD) medicines in the market. In this sense, there seems to be no unmet need that would otherwise justify the medical use of cannabis-based products. Interestingly, it has been observed that the adverse effects of cannabis-based products and medicinal cannabinoids used for short periods are similar to those of commonly used medicines. However, there is scarce data on the toxicological profiles of cannabis products sold in medical dispensaries (namely in the US and Canada), which may be used for longer periods (Hall et al., 2019). Moreover, the chronic use of these substances may interfere with important biological processes (e.g., neurogenesis) or induce epigenetic changes that may ultimately trigger the onset of neuropsychiatric disorders or cause the development of addiction.

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