Current controversies in medical cannabis: Recent developments in human clinical applications and potential therapeutics

Anne Katrin Schlag [a,b], Saoirse E. O'Sullivan [c], Rayyan R. Zafar [a,b], David J. Nutt [a,b,*]

[a] *Drug Science, London, UK*
[b] *Imperial College London, Du Cane Road, London, W12 0NN, UK*
[c] *Independent Consultant, UK*

ABSTRACT

Knowledge about the therapeutic potential of medical cannabis has greatly improved over the past decade, with an ever-increasing range of developments in human clinical applications. A growing body of scientific evidence supports the use of medical cannabis products for some therapeutic indications, whilst for others, the evidence base remains disputed. For this narrative review, we incorporate areas where the current evidence base is substantial, such as intractable childhood epilepsy and multiple sclerosis, as well as areas where the evidence is still controversial, such as PTSD and anxiety.

We provide a high-level summary of current developments using findings from recent major reviews, as well as real world evidence (RWE), including global database registries and other patient reported outcomes (PROs). On the one hand, our strongest empirical data supports the use of cannabis-based medicinal products (CBMPs) for conditions with relatively small patient numbers. Yet on the other hand, the conditions, where the highest patient numbers present, often have debatable clinical evidence but good RWE, incorporating PROs of 1000s of patients.

The discord between PROs and the respective strength of the evidence from randomised controlled trials (RCTs) highlights the urgent need for further research. The scientific literature examining the efficacy of medical cannabis for many conditions is still developing, whilst large numbers of patients globally have been successfully using medical cannabis to treat a broad range of conditions. We conclude on the importance of systematically developing RWE databases to supplement RCTs and to bridge the current evidence gaps.

1. Introduction

Cannabis is arguably the world's oldest medicine with examples of use found in many Eastern cultures thousands of years BC. Even today the Chinese character for anaesthesia is the same as that for cannabis. Cannabis was introduced into western medicine in the 1800s usually as an alcoholic tincture where its anti-epilepsy effects were noted and benefits for mental health reported (O'Shaughnessy, 1843; Reynolds, 1890). Medical cannabis remained in the UK pharmacopeia until 1971. In the USA and many other countries, cannabis was banned in the 1930s under the League of Nations report in an attempt to prevent recreational use. Since the early 2000s, most US states and over 20 countries have reinstated medical cannabis, and in December 2020, medical cannabis was finally removed from schedule 4 of the 1961 UN convention on narcotic drugs. In addition, medicines made of extracts of cannabis, in particular Sativex (Δ^9THC + CBD - for spasticity in MS) and Epydiolex (purified plant-derived CBD for some rare childhood epilepsies) have been licensed in some western countries. UK legislation has allowed medical cannabis preparations since November 2018, but very few prescriptions have been issued by the NHS. Despite this, it is estimated that over a million people are using illegally-sourced cannabis for self-medication of diagnosed conditions in the UK (Couch, 2020). Reasons for this are discussed in Nutt et al.'s (2020) recent review.

1.1. Aim of our narrative review

The aim of this narrative review is to provide a high-level summary of the current evidence base, including the most recent developments in

---

* Corresponding author. Drug Science, London, UK.
E-mail addresses: Anne.schlag@drugscience.org.uk (A.K. Schlag), canpharmaconsulting@gmail.com (S.E. O'Sullivan), r.zafar19@imperial.ac.uk (R.R. Zafar), d.nutt@imperial.ac.uk (D.J. Nutt).

human clinical applications and potential therapeutics, incorporating randomised controlled trials, RWE and PROs. This is no easy feat as both types of evidence are not always in agreement. We outline areas where the evidence base is strong, involving little controversy, and focus on areas where the evidence base is still disputed, as well as the potential future conditions for which cannabis might be prescribed.

1.2. Definitions

Cannabis-based medical products (CBMPs) can vary from purified single compounds (often THC or CBD), to complex mixtures of hundreds of molecules, in multiple formulations (oils, solutions, sublingual sprays, tablets and capsules), with multiple delivery mechanisms (oral, nasal, rectal, and inhalation). Table 1 summarises some of the current medical cannabis products that patients are using, their typical routes of administration and their typical indications. This table aims to highlight the heterogeneity in product types which can make the analysis of their efficacy through clinical trial and RWE data difficult due to the differences in the pharmacodynamics and pharmacokinetics of the products.

1.3. Entourage hypothesis

The cannabis plant makes over 100 cannabinoid molecules and several hundred terpenoids and flavonoids (Namdar et al., 2019). Whilst most research into the medicinal use of cannabis has focussed on the effects of the two major phytocannabinoids (THC and CBD), the past two decades have seen the observation of potential synergistic effects of other chemical entities of the cannabis plant that warrant further investigation. This possibility of multiple beneficial interactions between cannabinoids - the entourage effect-is increasingly supported by clinical observations.

The coining of the term the entourage effect was established in 1998 by Prof Mechoulam and Shimon Ben-Shabat who demonstrated that a range of seemingly inactive metabolites could alter the activity of the endocannabinoid system (Ben-Shabat et al., 1998). These findings gave rise to the idea of pharmacological synergy wherein the summation of effects was greater than the sum effect of individual molecules and in particular reference to botanical medicine supported the idea of whole plant extracts having a superior efficacy (Mechoulam and Ben-Shabat, 1999).

One observational study noted that a combination of both THC and CBD from whole plant extracts were necessary for reducing seizure frequency and superior to CBD alone in children suffering from various forms of epilepsy (Zafar et al., 2020). However, another study in autism did not find whole plant product to be superior to isolated cannabinoids when assessing behavioural and clinical outcomes, nonetheless there was a significantly higher rate of response on behavioural outcomes in the whole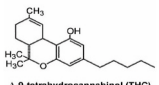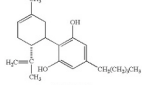-plant group (49%) versus placebo (21%) which show the utility of whole plant product in reducing behavioural issues related to autism (Aran et al., 2021). A meta-analysis of 670 patients showed significantly fewer severe adverse events and significantly higher proportion of participants achieving 50% or greater reduction in seizure frequency (71% vs 36%) in patients using CBD predominant cannabis extracts vs purified CBD (Pamplona et al., 2018). Such results possibly supporting the hypotheses of the synergistic contributions of phytocannabinoids and terpenes (Lewis et al., 2018) to superior therapeutic success, although head-to-head studies with products of similar formulation and route of delivery are required. In the management of intractable cancer-related pain an RCT indicated that a THC:CBD rich extract in equal amounts provided statistically significant reductions in mean pain Numerical Rating Scale (NRS) compared with placebo whereas THC-rich extract alone failed to provide sufficient pain relief indicating the elevated analgesic effects of combined cannabinoid therapy for this condition (Johnson et al., 2010).

The terpenoid caryophyllene, which is found in the cannabis plant, has been found to significantly reduce craving to cigarettes ($P < 0.01$). One purported mechanism is via CB2 receptor agonism, with caryophyllene being a CB2R agonist in its own right, thus indicating a conceivable new drug target for addiction (Rose and Behm, 1994). Further work has noted the ability of caryophyllene to inhibit cocaine addiction related behaviours through activation of specific biochemical pathways in the mesolimbic reward pathway, laying the groundwork for future in-human validation of such findings (Galaj et al., 2020). Indeed, there is a paucity of literature on the interaction of terpenes and phytocannabinoids with Santiago et al. (2019) reporting that the 6 most common terpenes do not affect THC mediated signalling at cannabinoid receptors. In spite of this, the independently reported pharmacological activity of terpenes could theoretically provide adjunctive therapeutic value to cannabinoids that are known to have clinical efficacy. Whilst the individual in-vitro effects of terpenes are supportive of its purported role in mood and addiction, translational efficacy has not yet been determined and controlled clinical research in this field remains sparse.

Anecdotally, there is much evidence to support the role of whole plant cannabis as this is what the majority of medical cannabis patients consume as opposed to pharmacologically purified compounds used in RCTs. Whilst there is some evidence on cannabinoid-cannabinoid interactions, further enquiry is needed to investigate conflicting results from both in-vitro and animal studies of the interaction between phytocannabinoids and terpenes. Such scrutiny of the entourage hypothesis is required in order to fully understand the true pharmacological properties of cannabis (please see Cogan, 2020). The demonstration of the synergy of THC and CBD in modulating therapeutic outcomes in clinical populations, as seen in epilepsy and pain, plus the utility of terpenes to therapeutically modulate brain pathways involved in mood and substance use disorders in animal models, provide some support to the theory of the entourage effect. Given different cultivars of the cannabis

Table 1

Cannabis based medicines include a wide variety of product types from single active pharmaceutical ingredient (API, e.g. THC or CBD) to complex mixtures of 100s of molecules, which are also consumed/administered through a variety of routes.

	THC products	Purified CBD	CBD:THC ratios	Whole flower products	Enriched products
Active pharmaceutical ingredients	Δ-9-tetrahydrocannabinol (THC)	Cannabidiol (CBD)	Often 1:1 but 20:1 and 50: products becoming popular in neurological conditions	100s molecules; phytocannabinoids, flavonoids, terpenes. Modern medicinal products have specified THC:CBD ratios.	THC or CBD dominant products with a % (variable) of other phytochemicals
Typical examples	Nabilone (THC analogue) and Dronabinol (synthetic THC-Senzer; Candex)	Epidiolex; Zygel; ClaraCeed	Sativex (1:1); Cellen Satoline- various ratios; Lyphe Group Noidecs- various ratios	Khiron flower, Lyphe Noidecs flower, Cellen Satoline flower; Bedrocan various flowers	Lyphe Noidecs, Bod Aus Medicabalis
Typical routes of administration	Oral (tablets, capsules, solution), inhaled	Oral solution, tablets, capsules, gels	Sublingual spray, oils	Smoked, vaporised, inhaled, edibles, oils	
Typical indications	CINV, appetite stimulation, pain	Intractable epilepsy, Fragile X syndrome	Multiple sclerosis, pain, intractable epilepsy	Pain, anxiety, sleep, intractable epilepsy	

plant have different amounts and combinations of these components, research is difficult and still limited and so outside the scope of this review.

2. Developing the clinical evidence base

Since the isolation of the active ingredients of cannabis, and the discovery of the cannabinoid receptors and the endocannabinoid system, there has been a huge growth in clinical trials investigating the efficacy of CBMPs (see Fig. 1). The relative lack of clinical trials before 2000 highlights the importance to also include RWE to further build up the evidence base.

3. Summarising the current evidence

Despite the extensive changes in global policy on CBMPs, there is only limited conclusive evidence regarding its short- and long-term health effects (both harms and benefits). The previous schedule 1 status of cannabis, together with the lack of private or public funding, resulted in the absence of high-quality research, meaning that for many conditions, essential information of the health implications of CBMPs is still developing.

For our summary, we incorporate areas where the current evidence base is substantial and generally undisputed, such as intractable epilepsy and multiple sclerosis, as well as areas where the evidence is still controversial and often based on RWE and PROs such as in psychiatric conditions, including PTSD and anxiety.

We provide a high level summary using findings from recent major reviews (e.g. Whiting et al., 2015; NASEM, 2017), as well as global databases of RWE (see Table 2 for examples), including observational and case study reports. The specific conditions are covered in depth by other authors in this special issue. These evidence sources highlight a major controversy. On the one hand, our strongest empirical data supports the use of CBMPs for conditions with relatively small patient numbers. Yet on the other hand, the conditions, where the highest patient numbers present, often have debatable empirical evidence but good RWE, often incorporating PROs of 1000s of patients.

Fig. 2 summarises the strength of the current evidence relative to the estimated number of patients using CBMPs for a certain condition. Our summary is based on collective knowledge and understanding and includes RWE/PROs in addition to the scientific evidence base. Integrating results from RCTs with the wealth of observational data necessarily means that our graph is based on generalisations of the whole class of medical cannabis, including products acquired through the illicit market, with all the risks and limitations this may entail. Whilst we categorise the evidence into four distinct groups for ease of representation, i.
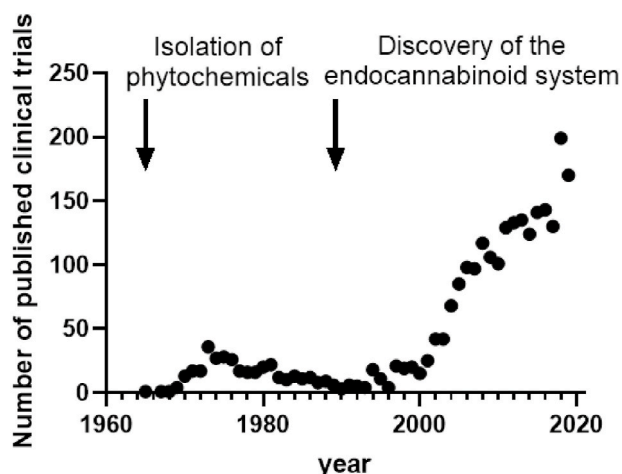
e. squares on Fig. 2, there is of course variation within each category, indicated by the location in each square.

3.1. High strength of evidence - low number of patients

There is conclusive or substantial evidence that CBMPs are effective as treatment for intractable epilepsy, multiple sclerosis (MS), cancer-related nausea, and appetite stimulation in wasting disorders (NASEM, 2017; Whiting et al., 2015), which is unsurprising given that these are conditions for which there are licensed cannabis-based products available. The strength of evidence to support the use of CBPMs to treat inflammatory bowel disorders (IBD) is also relatively high (Picardo et al., 2019).

These findings are corroborated by recent PROs and RWE studies (e. g. Schmidt-Wolf and Cremer-Schaeffer, 2019; Couch, 2020; Minnesota Department of Health, 2020; Zafar et al., 2020) showing the use of CBMPs for these conditions. Especially the use of medical cannabis for improving symptoms of inflammatory bowel disease is increasing (Benson et al., 2020; Naftali et al., 2019).

3.2. High strength of evidence - high number of patients

Overall, there is a high strength evidence base supporting the use of CBMPs for the treatment of neuropathic pain, cancer-related pain and chronic pain, which are conditions affecting a high number of patients. A review by the National Academies of Sciences, Engineering and Medicine (NASEM, 2017) found the evidence base for chronic pain to be 'substantial'. Using a Multi-Criteria-Decision-Analysis (MCDA) approach to assess the benefits and safety of various CBMPs to treat chronic neuropathic pain, Nutt et al. (2021) found that medical cannabis is among the most preferred treatments for people with long term, problematic neuropathic pain.

On the other hand, the International Association for the Study of Pain (IASP, 2021) does not endorse the general use of cannabinoids to treat pain, due to a lack of evidence from high quality research. Nevertheless, Prof Andrew Rice, chair of IASP, also stresses that this assessment should not dismiss the lived experience of pain patients who have found benefits from the use of CBMPs.

RWE, including large scale databases and surveys, consistently show that these pain conditions are by far the most common conditions cannabis is used for by patients (e.g. BfArm database, Minnesota database; T21; Couch, 2020; UPA, 2018). Currently, up to 90% of patients in state-level medical cannabis registries list chronic pain as their qualifying condition for the medical program (Wiese and Wilson-Poe, 2018).

Additionally, an increasing number of observational studies highlight that CBMPs may be used as an alternative treatment for intermittent or chronic opioid users to mitigate their pain. In Takakuwa's et al. (2020) long-term observational study of 180 patients with back pain, cannabis use worked as an alternative to prescription opioids in over half the patients and helped diminish opioid use in some. Other studies have also found that access to CBMPs for chronic pain decreases opioid use by 40–60% and patients report they prefer cannabis to opioids (Boehnke et al., 2016; Reiman et al., 2017).

However, recent meta-analyses and systematic reviews on the use of cannabis to treat chronic pain are less supportive (e.g. Stockings et al., 2018) and the current RCT evidence is still often regarded as 'inconclusive' (Häuser et al., 2018; Whiting et al., 2015) probably because they fail to adequately assess or include PROs. It should also be noted that RCTs often use pain ratings as the primary outcome in their trials. Cannabis does not just affect pain *per se,* but the overall quality of life of the patient (Lavie-Ajayi et al., 2019; Nutt et al., 2021), which is not reflected in whether an RCT is deemed as being successful.

3.3. Low strength of evidence - low number of patients

At present, the category supported only by low strength evidence for

Fig. 1. Number of published clinical trials.

Table 2
Databases and surveys.

Database/survey	Details
Bfarm (Germany)	In Germany, physicians inform the BfArM about the prescriptions for medical cannabis and the respective results on the patient side, documenting information concerning the indications they have prescribed cannabis for, the concentration of the prescribed product, and how patients responded to the therapy. The BfArM conducts a large non-interventional observational study by collecting all of this data. Results showed that there is an overwhelming prescription of medical cannabis for chronic pain patients. Of 6538 patients, 69% were prescribed medical cannabis to treat chronic pain. https://www.bfarm.de/DE/Bundesopiumstelle/Cannabis/Begleiterhebung/_node.html
Minnesota (USA)	Minnesota's Medical Cannabis patient registry database (established July 2015) currently has data from 25,356 patients, enrolled for a broad variety of conditions, including terminal illness (accompanied by severe or chronic pain, nausea, or severe wasting), and Amyotrophic Lateral Sclerosis (ALS or Lou Gehrig's Disease). The vast majority of patients are enrolled for intractable pain (62%), followed by PTSD (24%). 67.2% of the 25,356 patients are currently certified for more than one condition. https://www.health.state.mn.us/people/cannabis/docs/about/quarupdates/oct2020.pdf
CB2 (USA)	Mahabir et al. (2020) used a retrospective database analysis (CB2 Insights) of over 60.000 US patients to investigate medical cannabis use in the US. The top three mutually exclusive primary medical conditions reported were unspecified chronic pain (38.8%), anxiety (13.5%) and post-traumatic stress disorder (PTSD) (8.4%). The average number of comorbid conditions reported was 2.7, of which anxiety was the most common (28.3%). Females reported significantly more comorbid conditions than males (3.1 compared to 2.3). This study highlights the range and number of conditions for which patients in the US seek medical cannabis. https://cb2insights.ca/data https://jcannabisresearch.biomedcentral.com/articles/10.1186/s42238-020-00038-w
Project T21 (UK)	Project Twenty 21 is a UK registry, recently launched by the charity Drug Science, aiming to monitor the health outcomes of 20,000 patients using cannabis based medicinal products (CBMPs), creating the largest body of evidence in Europe for the safety and efficacy of CBMPs. So far, over 50% of patients are registering for pain, with 35% coming to use CBMPs to treat their anxiety. As the database matures, T21 will continue to highlight conditions and record their success of treatment. https://www.drugscience.org.uk/twenty21-is-now-live/
Quebec Registry (Canada)	The Quebec registry for users of dried medical cannabis (established 2015) aims to include 3000 patients until 2025 https://registrecannabisquebec.com/en The database is based on the planned collection of observational data for a total of 10 years, with collection of clinical data for 4 years following the recruitment of each participant.
Medical Cannabis Registry (Denmark)	A three-stage register based evaluation is underway of the effects and adverse effects on various CBMPs. Results are expected in 2021.
Cohort Safety Study (Canada)	Ware at al. (2015) studied cannabis for the management of chronic pain in a safety study (COMPASS). Compared with the baseline, a significant reduction in average pain intensity over 1 year was observed in the cannabis group. The sensory component of pain was reduced over 1 year in cannabis users compared with the controls.
UK Medical Cannabis Registry (UK)	The UK Medical Cannabis Registry was established by Sapphire Medical Cannabis Clinics in 2020. It is a prospective registry designed to collate outcomes on medical cannabis prescribing. Anonymised data will be made available to the medical community upon request. https://www.ukmedicalcannabisregistry.com
Nationwide Survey (UK)	Ware et al. (2005) conducted a nationwide UK survey comprising a self-selected sample of 2969 patients. Medicinal cannabis use was reported by patients with chronic pain (25%), multiple sclerosis and depression (22% each), arthritis (21%) and neuropathy (19%).
Online Survey (US)	Sexton et al. (2016) conducted an anonymous online survey of 1429 participants identified as medical cannabis users. The most frequently reported conditions for which they used Cannabis were pain (61.2%), anxiety (58.1%), depression (50.3%), headache/migraine (35.5%), nausea (27.4%), and muscle spasticity (18.4%).
Pain E-Registry (Germany	Ueberall et al. (2019) provide an exploratory analysis of anonymised 12-week routine/open-label data provided by the German Pain e-Registry (GPR) on adult severe chronic pain patients treated with THC:CBD oromucosal spray. THC:CBD oromucosal spray proved to be an effective and well-tolerated add-on treatment for patients with refractory chronic pain, especially of neuropathic origin.
Questionnaire Study (Israel)	Habib et al. (2018) report results of 26 fibromyalgia patients from two hospital registries. There was a significant improvement based on Revised Fibromyalgia Impact Questionnaire Responses, with 50% of patients able to stop medications for fibromyalgia.
Cannabis as Medicine Survey 2020, 2018; 2016 (Aus)	The Cannabis as Medicine Survey (https://redcap.sydney.edu.au/surveys/?s=D387MRCWH3) survey lists the conditions patients used cannabis for, as well as patients' experiences of benefits and side effects, as well as other drug use. In 2018, data were available for 1388 respondents. The main categories of condition being treated with medical cannabis were pain (36.4%), mental health (32.8%), sleep (9.2%), neurological (5.2%) and cancer (3.8%) (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7278204/In 2016, 1748 participants reported high levels of clinical effectiveness as well as frequent side effects. The main conditions treated were anxiety (50.7%), back pain (50.0%), depression (49.3%), and sleep problems (43.5%) https://pubmed.ncbi.nlm.nih.gov/30092752/
UPA Survey 2018 (UK)	This survey of PROs of 1765 patients showed that the majority of patients used medical cannabis to treat their pain and fibromyalgia, followed by anxiety and depression. 76% of patients reported significant improvement which compared to the 8.8% that reported the same on prescription medication. https://www.upalliance.org/patient-survey-2018
CMC Survey (UK)	This nationally representative online survey of 10602 adults highlighted that the majority of respondents used medical cannabis to treat depression, high blood pressure, and anxiety, followed by arthritis and chronic pain. A high proportion of the disease population also used cannabis to treat symptoms of PTSD and schizophrenia. https://static1.squarespace.com/static/5f1ebab9df1a5a6c6f4a9fd0/t/5f2afa4c0537ee75262d8157/1596652117375/Left+Behind.pdf
Altaflora App (UK)	Alta Flora analyzes anonymised data on medical cannabis prescriptions registered with MedCannID, providing a unique insight into the current state of medical cannabis in the UK as the first cross-market look at medical cannabis prescription data. Pain was the most commonly prescribed condition (46%), followed by fibromyalgia (21%), and psychological conditions (16%) https://alta-flora.com/en/blog/two-years-on-what-does-the-data-say/
Cannabis à usage medical programme (France)	A French registry of medical cannabis use, supported by the Agency for the Safety of Medicines and Health Products (ANSM), is scheduled to begin in 2021, aiming to collate data of 3000 patients over two years. https://www.ansm.sante.fr/Dossiers/Cannabis-a-usage-medical/Appel-a-candidatures-fourniture-et-distribution-de-medicaments-a-base-de-cannabis-pour-l-experimentation/(offset)/0#

the use of CBMPs includes the widest range of conditions, most of which affect relatively low number of patients but for whom there is some limited proof of concept RCT or observational data to support the use of CBMPs that warrants more research.

● Parkinson's Disease
● Tourette's Syndrome
● Skin conditions
● Fibromyalgia
● Glaucoma
● Dementia
● Autism Spectrum Disorders (ASD)
● ADHD
● Substance Use Disorders (SUD)
● PTSD
● Migraine
● Schizophrenia

In relation to Fibromyalgia, one of the most common chronic pain conditions treated with CBMPs by patients Alta Flora, 2020, a recent RCT found that the cannabis group presented a significant decrease in Fibromyalgia Impact Questionnaire (FIQ) score in comparison with the placebo group (Chaves et al., 2020).

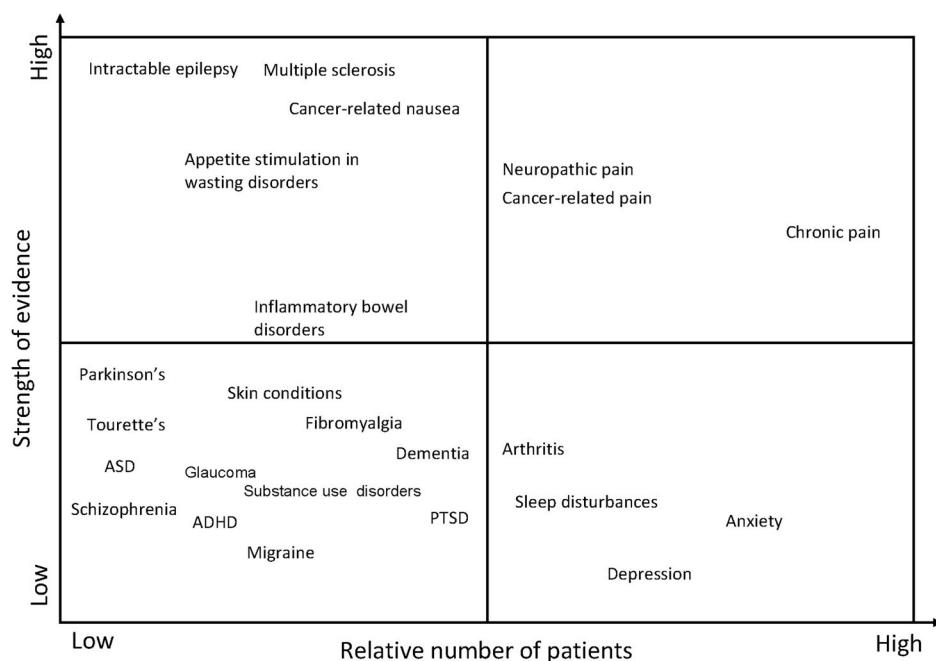A recent RCT of nabilone (0.25 mg before bedtime for three nights,

Fig. 2. Strength of evidence versus prevalence of use.

then titrated up to 0.5 mg/day for the next 4 days, and up to 1–2 mg/day the following weeks) in moderate to severe Alzheimer's disease, found it effective in the agitation and neuropsychiatric symptoms, although it also had sedative and cognitive side effect (Hermann et al., 2019). Pre-clinical research indicates that especially the non-psychoactive cannabinoids are potential lead drug candidates for Alzheimer's disease and other neurodegenerative diseases (Schubert et al., 2019).

Whilst the evidence of medical cannabis efficacy for ASD and ADHD so far is minimal (Cooper et al., 2017) RWE indicates that patients are treating ADHD with CBMPs (Bfarm; Minnesota database), and the anecdotal evidence of successful medical cannabis treatment for autism spectrum disorder (ASD) is accumulating (e.g. Aran et al., 2019; Bar-Lev Schneider et al., 2019; Fusar-Poli et al., 2020).

The antipsychotic actions of CBD have been extensively reviewed (e. g. Jacobson et al., 2019) and cannabis is frequently reported to be used as self-medication to treat schizophrenia (e.g. Couch, 2020; T21). A current RCT is investigating whether cannabis and the cannabinoid agonist dronabinol (3–5% tetrahydrocannabinol cannabis cigarette and dronabinol 15 mg 3–5% by mouth), given in low dose to patients with schizophrenia and co-occurring cannabis use disorder, could ameliorate the brain reward circuit dysregulation in these patients and, thereby, provide evidence in support of the role of cannabis as a "self--medication" agent for them. (ClinicalTrials.gov Identifier: NCT01964404). CBD has also been investigated as an adjunct to anti-psychotic treatment and in a recent double-blind parallel trial of 1000 mg of CBD a day, participants receiving CBD saw significant reductions in their positive symptoms of psychosis, and greater improvements on clinical global impressions scale scores (McGuire et al., 2018).

A growing number of patients also report treating their PTSD with CBMPs (e.g. Couch, 2020; Minnesota database), and in their systematic review on the effectiveness of cannabinoids in the treatment of PTSD, Hindocha et al. (2019) found that cannabinoids may decrease PTSD symptomology, particularly sleep disturbances and nightmares. However, most of the studies were small and assessed to be of low quality. Elms et al. (2019) retrospective case series of 11 adult patients concluded that the administration of oral CBD was associated with PTSD symptom reduction in their patients, specifically in relation to frequent nightmares.

There is increasing evidence to support the use of CBMPs for treatment of Substance Use Disorders (SUD). For example, Freeman et al. (2020) RCT of CBD to treat Cannabis Use Disorder showed efficacy especially at 400 m/d. An open-label clinical trial supports this finding (Solowij et al., 2018).

Wiese and Wilson-Poe (2018) highlight the potential for CBMPs as an adjunct or alternative treatment for opioid use disorder, demonstrating their potential (amongst others) to ease withdrawal symptoms and cravings as well as reducing overdose deaths.

3.4. Low strength of evidence-high number of patients

Prescription registries reveal large numbers of patients are using CBMPs to treat their arthritis, sleep disturbances, depression and anxiety. Mahabir et al. (2020) found that second to unspecified chronic pain, patients were most likely to report anxiety as their primary medical condition, and anxiety was the most commonly reported comorbid condition. Similarly, Sexton et al. (2016) found that the second and third most common medical conditions that patients reported using medical cannabis for were anxiety (58.1%) and depression (50.3%).

Anxiety is regularly one of the most frequent conditions, for which cannabis is used by patients (Couch, 2020; T21; UPA, 2018). Especially in relation to CBD only products, PROs stress their prevalent use for anxiety and anxiety related disorders (e.g. Leas et al., 2020). CBD is predominantly anxiolytic and has benefits to treat anxiety disorders (Blessing et al., 2015). A pilot trial is currently underway to investigate the effect of 25 mg full-spectrum CBD soft gel capsules (up to a total dosage of 100 mg per day) on individuals with diagnosed anxiety (ClinicalTrials.gov Identifier: NCT04267679).

To date, there is only limited RCT evidence for the treatment with CBMPs for depression, yet in most RWE databases and surveys (e.g. Couch, 2020; UPA, 2018), many depressive patients are self-medicating with cannabis perhaps because depression is secondary to other chronic disorders, such as MS and pain (Fernandez-Ruiz et al., 2020).

Black et al. (2019) conclude that there is some evidence to support the use of CBMPs to treat the above psychiatric applications and stress that there is only very low-quality evidence that pharmaceutical THC (with or without CBD) leads to a small improvement in symptoms of anxiety among individuals with other medical conditions. This stark divergence between RWE, incorporating large numbers of PROs, and

limited RCT evidence highlights the urgent need for further systematic research in these areas.

3.5. Supporting pre-clinical data

Underpinning the clinical evidence base for the medicinal benefits of cannabis and its constituent chemicals, is a very strong literature exploring the molecular targets and mechanism of action of phytocannabinoids for most of the common indications for which cannabis-based medicines are used. However, there are caveats to the translatability of some of this research. For example, most preclinical research examines the effects of pure phytochemicals which is relevant for the clinical use of pure THC or CBD far more patients use cannabis extracts that are a mix of phytocannabinoids that are less well studied preclinically. Some studies have looked at simple combinations of pure phytocannabinoids, e.g. the combination of THC and CBD in a 1:1 ratio (like Sativex (nabiximols)) and found this is superior to the effects of either compound alone in preclinical models of neuropathic pain (King et al., 2017) or epilepsy (Samarut et al., 2019). However, it is yet to be established what the most effective combination of THC and CBD would be in different disorders. Some registered trials are looking at 3:1 (THC: CBD, ClinicalTrials.gov Identifier: NCT04042545) in cancer pain and 1:20 (THC:CBD, ClinicalTrials.gov Identifier:NCT03024827) in epilepsy. Other combinations of phytocannabinoids that preclinical data has shown superiority include (but are not limited to) the combination of cannabinol (CBN) and CBD (1:1 and 5:1; Wong and Cairns, 2019). CBDA and THC (1:1000; Rock et al., 2018) (both in analgesia). The exact ratio and combination of phytochemicals is likely to be different for different disease indications, and much further research is required.

3.5.1. Progress in human trials in minor cannabinoids

While preclinical data is beginning to show us the potential of minor phytocannabinoids, published clinical research (either at case report or clinical trial level) in this area is still lacking.

GW Pharmaceuticals investigated the potential of purified THCV on its own, or in combination with CBD, in patients with type 2 diabetes (Jadoon et al., 2016). While THCV (5 mg twice daily) reduced fasting blood glucose levels in these patients in this phase 2 study, results of a dose-ranging follow up study (ClinicalTrials.gov Identifier: NCT02053272) have not been published or posted, and this is no longer in the GW pipeline.

Off the back of successful preclinical studies, GW Pharmaceuticals trialled CBDV in adult epilepsy, however the study did not meet its primary endpoint of seizure reduction. Purified CBDV is still being pursued to reduce behavioural symptoms in children and young adults with Prader Willi Syndrome (10 mg/kg/day, NCT03848481) and in autism (NCT03202303 and NCT03849456).

3.5.2. Future applications

In the current COVID-19 pandemic, many researchers have considered repurposing medicines known for their anti-viral or anti-inflammatory properties to tackle this global issue (or indeed future similar viruses). Researchers have hypothesised that CBD could be used as an anti-viral agent (Hill, 2020) or anti-inflammatory (Byrareddy and Mohan, 2020; Costiniuk and Jenabian, 2020) tool, or to inhibit pulmonary fibrosis in COVID-19 patients (Esposito et al., 2020).

Experimental evidence has shown that CBD is capable of down-regulating the expression of key receptors (ACE2 and TMPRSS2) for SARS-CoV2 in human epithelial cells (Wang et al., 2020). CBD also downregulates the cytokine storm seen in acute respiratory distress syndrome (ARDS) induced by viral infection in a murine model of the mechanisms of SARS-CoV-2 (Khodadadi et al., 2020), which has been attributed to its upregulation of apelin (Salles et al., 2020).

Because of the known growing evidence of the anxiolytic effects of CBD, it has also been hypothesised that CBD could be used as a therapeutic option to treat the long-lasting COVID-19-related anxiety and

PTSD (O'Sullivan et al., 2020), which will be a significant issue of the pandemic. A clinical trial testing this hypothesis is registered assessing 28 days treatment with CBD (300 mg) in the treatment of burnout and distress in frontline healthcare professionals (NCT04504877).

In addition to the use of phytocannabinoids in COVID-19, pharmaceutical companies are trialling the potential of the endocannabinoid-like molecule palmitoylethanolamide (FSDPharma; ClinicalTrials.gov Identifier: NCT04619706) and a synthetic CB2 agonist (TetraBioPharma).

Apart from COVID-19, there are a range of other novel indications for CBMPs in clinical research, not (yet) included in Fig. 2 but under clinical investigation. Looking at clinicaltrials.gov, these are some areas that are in phase 2 or 3: endometriosis (NCT04527003, NCT04527003), Blepharospasm (NCT04423341), Hallux Disorders (NCT04103814), Trichotillomania (NCT03530800), muscle injury (NCT04586712), Graft-Versus-Host Disease (GVHD) (NCT03840512), Motor Neuron Disease (NCT03690791) and Hidradenitis Suppurativa (NCT03929835).

4. Why is the evidence base still often controversial and how can this be addressed?

For many of the conditions CBMPs are currently used for by patients, the RCT evidence for efficacy is still limited and inconclusive for many reasons. Reasons include lack of phase 3 trials (too expensive if not for the development of licensed medication and the perceived resistance of regulatory to approve cf the Sativex example), lack of government funding around this research, difficulties in interpreting the current evidence base because of the variety of compounds and lack of good health economic analyses.

The lack of clinical and regulatory confidence in CBMPs is in stark contrast with the many patient testimonies (both in the UK and in other countries), as well as large scale observational studies where medical cannabis is seen as an important addition to their treatment (e.g. Couch, 2020; T21; UPA, 2018). Many patients experience therapeutic satisfaction when using pharmaceutical cannabis, especially in relation to pain alleviation (Brunt et al., 2014) and report improvements in or relief of a range of symptoms, as well as the ability to reduce or stop other medications (Stith et al., 2019).

Whilst there are concerns by physicians and policy-makers about perceived lack of RCT evidence for many conditions, the perceptions that RCTs are the only objective, valid evidence needs to be widened in relation to CBMPs (Nutt et al., 2020), in order to bring this evidence more in line with real life patient experience. Kessler and Glasgow (2011) propose a major paradigm shift away from the gold standard of RCTs to be able to produce research with more rapid clinical, public health and policy impact. Such a shift should include more relevant evidence and have a greater focus on the needs of practitioners and patients (Kessler and Glasgow, 2011). In relation to CBMPs, current RWE databases already have (and likely will continue to) generated huge amounts of evidence for their use, often for conditions for which RCT evidence is still lacking or may never be obtained.

The RWE shown above is now building up to a pattern of evidence, emphasizing the effectiveness of using medical cannabis to treat pain syndromes as well as various psychiatric conditions. Including 'qualitative' evidence does not diminish the value of RCTs but rather complement them and serve as a precursor to later studies (Nutt et al., 2020).

Using RWE of course also has limitations, not least the lack of homogeneity between databases. Future research might aim to rectify this, systematically providing exact numbers of patients, conditions and side effects. The recent Health Innovation Conference (Nov 2020)[1] focused on the European Health Data Space and stressed that RWE is indeed necessary for better access to new important medicines, of which

---

[1] https://rwe4decisions.com/event/health-innovation-the-european-health-data-space-and-real-world-evidence/.

cannabis is certainly one. Ideally there should be a network of databases, with international guidelines for collecting RWE on CBMPs. Our present summary already shows many similarities between databases, and a network of databases could build up to a pattern of evidence which is larger than the sum of its parts.

5. Conclusions

Medical cannabis exerts numerous therapeutic effects, as it has antispastic, analgesic, antiemetic, neuroprotective, and anti-inflammatory actions. Cannabis in its many forms has vast untapped potential for human clinical applications, as it is a medicine which can be highly personalised.

By including RWE, we highlight the conditions that patients are seeking CBMPs for most often. Most of these applications would benefit from further clinical evidence. Because of the lack of RCT evidence, it is important to incorporate RWE and PROs which might show avenues for future applications. Unlike with other medicines, the development of medical cannabis has been driven by patient use with reported benefits, with science, industry and policy-makers having to catch up.

Rigorous clinical trials investigating the use of medical cannabis to treat various conditions, including psychiatric conditions such as anxiety, insomnia, depression and PTSD are still required and likely would benefit a large number of patients especially as many of the conditions are lacking satisfactory treatments currently. In the meantime, there is also a need to develop further guidance for prescribers. Simultaneously, it is vital to further mature current databases, such as T21, BFarm, and initiate the new French registry proposed for 2021 to develop longitudinal real life outcome data.

Author contributions

AKS developed the initial draft of the manuscript. S'OS developed the figures. All authors made substantial contributions to the conception and design of the review, and subsequent revisions and all approved the final version to be submitted.

Funding source

Declaration of competing interest

AKS is Head of Research of the charity Drug Science, which receives an unrestricted educational grant from a consortium of medical cannabis companies. DJN is chair of Drug Science, and RRZ is intern at Drug Science. SO'S is an independent consultant working with several pharmaceutical companies developing cannabis based medicines.

References

Alta Flora, 2020. Two years on- what does the data say? https://alta-flora.com/en/blog/two-years-on-what-does-the-data-say/ [accessed May 5th 2021].

Aran, A., Cassuto, H., Lubotzky, A., Wattad, N., Hazan, E., 2019. Brief report: cannabidiol-rich cannabis in children with autism spectrum disorder and severe behavioral problems—a retrospective feasibility study. J. Autism Dev. Disord. 49, 1284–1288. https://doi.org/10.1007/s10803-018-3808-2.

Bar-Lev Schleider, L., Mechoulam, R., Saban, N., Meiri, G., Novack, V., 2019. Real life experience of medical cannabis treatment in autism: analysis of safety and efficacy. Sci. Rep. 9 https://doi.org/10.1038/s41598-018-37570-y.

Ben-Shabat, S., Fride, E., Sheskin, T., Tamiri, T., Rhee, M.H., Vogel, Z., Bisogno, T., De Petrocellis, L., Di Marzo, V., Mechoulam, R., 1998. An entourage effect: inactive endogenous fatty acid glycerol esters enhance 2-arachidonoyl-glycerol cannabinoid activity. Eur. J. Pharmacol. 353 (1), 23–31. https://doi.org/10.1016/s0014-2999(98)00392-6.

Benson, M.J., Abelev, S.V., Connor, S.J., Corte, C.J., Martin, L.J., Gold, L.K., Suraev, A.S., McGregor, I.S., 2020. Medicinal cannabis for inflammatory bowel disease: a survey of perspectives, experiences, and current use in Australian patients. Crohn's Colitis 360 2 (2). https://doi.org/10.1093/crocol/otaa015.

Bfarm. https://www.bfarm.de/DE/Bundesopiumstelle/Cannabis/Begleiterhebung/_node.html. (Accessed 5 May 2021).

Black, N., Stockings, E., Campbell, G., Tran, L.T., Zagic, D., Hall, W.D., Farrell, M., Degenhardt, L., 2019. Cannabinoids for the treatment of mental disorders and symptoms of mental disorders: a systematic review and meta-analysis. The Lancet Psychiatry 6, 995–1010. https://doi.org/10.1016/S2215-0366(19)30401-8.

Blessing, E.M., Steenkamp, M.M., Manzanares, J., Marmar, C.R., 2015. Cannabidiol as a Potential Treatment for Anxiety Disorders. Neurotherapeutics. https://doi.org/10.1007/s13311-015-0387-1.

Boehnke, K.F., Litinas, E., Clauw, D.J., 2016. Medical cannabis use is associated with decreased opiate medication use in a retrospective cross-sectional survey of patients with chronic pain. J. Pain 17, 739–744. https://doi.org/10.1016/j.jpain.2016.03.002.

Brunt, T.M., Van Genugten, M., Höner-Snoeken, K., Van De Velde, M.J., Niesink, R.J.M., 2014. Therapeutic satisfaction and subjective effects of different strains of pharmaceutical-grade cannabis. J. Clin. Psychopharmacol. 34, 344–349. https://doi.org/10.1097/JCP.0000000000000129.

Byrareddy, S.N., Mohan, M., 2020. SARS-CoV2 induced respiratory distress: can cannabinoids be added to anti-viral therapies to reduce lung inflammation? Brain Behav. Immun. 87, 120–121. https://doi.org/10.1016/j.bbi.2020.04.079.

Chaves, C., Bittencourt, P.C.T., Pelegrini, A., 2020. Ingestion of a THC-rich cannabis oil in people with Fibromyalgia: a randomized, double-blind, placebo-controlled clinical trial. Pain Med. 21, 2212–2218. https://doi.org/10.1093/pm/pnaa303.

Cogan, P., 2020. The 'entourage effect' or 'hodge-podge hashish': the questionable rebranding, marketing, and expectations of cannabis polypharmacy. Expet Rev. Clin. Pharmacol. 13 (8), 835–845. https://doi.org/10.1080/17512433.2020.1721281.

Cooper, R.E., Williams, E., Seegobin, S., Tye, C., Kuntsi, J., Asherson, P., 2017. Cannabinoids in attention-deficit/hyperactivity disorder: a randomised-controlled trial. Eur. Neuropsychopharmacol 27, 795–808. https://doi.org/10.1016/j.euroneuro.2017.05.005.

Costiniuk, C.T., Jenabian, M.A., 2020. Acute inflammation and pathogenesis of SARS-CoV-2 infection: cannabidiol as a potential anti-inflammatory treatment? Cytokine Growth Factor Rev. https://doi.org/10.1016/j.cytogfr.2020.05.008.

Couch, D., 2020. Left behind: the Scale of Illegal Cannabis Use for Medicinal Intent in the UK. Centre for Medicinal Cannabis, London.

Elms, L., Shannon, S., Hughes, S., Lewis, N., 2019. Cannabidiol in the treatment of post-traumatic stress disorder: a case series. J. Alternative Compl. Med. 25, 392–397. https://doi.org/10.1089/acm.2018.0437.

Esposito, G., Pesce, M., Seguella, L., Sanseverino, W., Lu, J., Corpetti, C., Sarnelli, G., 2020. The potential of cannabidiol in the COVID-19 pandemic. Br. J. Pharmacol. 177, 4967–4970. https://doi.org/10.1111/bph.15157.

Freeman, T.P., Hindocha, C., Baio, G., Shaban, N.D.C., Thomas, E.M., Astbury, D., Freeman, A.M., Lees, R., Craft, S., Morrison, P.D., Bloomfield, M.A.P., O'Ryan, D., Kinghorn, J., Morgan, C.J.A., Mofeez, A., Curran, H.V., 2020. Cannabidiol for the treatment of cannabis use disorder: a phase 2a, double-blind, placebo-controlled, randomised, adaptive Bayesian trial. The Lancet Psychiatry 7, 865–874. https://doi.org/10.1016/S2215-0366(20)30290-X.

Fusar-Poli, L., Cavone, V., Tinacci, S., Concas, I., Petralia, A., Signorelli, M.S., Díaz-Caneja, C.M., Aguglia, E., 2020. Cannabinoids for people with asd: a systematic review of published and ongoing studies. Brain Sci. 10 (9), 1–18. https://doi.org/10.3390/brainsci10090572.

Galaj, E., Bi, G.H., Moore, A., et al., 2021. Beta-caryophyllene inhibits cocaine addiction-related behavior by activation of PPARα and PPARγ: repurposing a FDA-approved food additive for cocaine use disorder. Neuropsychopharmacology 46, 860–870. https://doi.org/10.1038/s41386-020-00885-4.

Habib, G., Artul, S., 2018. Medical cannabis for the treatment of Fibromyalgia. JCR J. Clin. Rheumatol. 24.

Häuser, W., Finn, D.P., Kalso, E., Krcevski-Skvarc, N., Kress, H.G., Morlion, B., Perrot, S., Schäfer, M., Wells, C., Brill, S., 2018. European Pain Federation (EFIC) position paper on appropriate use of cannabis-based medicines and medical cannabis for chronic pain management. Eur. J. Pain 22 (9), 1547–1564. https://doi.org/10.1002/ejp.1297 (United Kingdom).

Hindocha, C., Cousijn, J., Rall, M., Bloomfield, M.A.P., 2020. The effectiveness of cannabinoids in the treatment of posttraumatic stress disorder (PTSD): a systematic review. J. Dual Diagn. 16 (1), 120–139. https://doi.org/10.1080/15504263.2019.1652380.

International Association for the Study of Pain (IASP), 2021. Presidential Task Force on Cannabis and Cannabinoid Analgesia Position Statement. Pain, Publish Ahead of Print. https://doi.org/10.1097/j.pain.0000000000002265.

Jacobson, M.R., Watts, J.J., Boileau, I., Tong, J., Mizrahi, R., 2019. A systematic review of phytocannabinoid exposure on the endocannabinoid system: implications for psychosis. Eur. Neuropsychopharmacol 29 (3), 330–348. https://doi.org/10.1016/j.euroneuro.2018.12.014.

Jadoon, K.A., Ratcliffe, S.H., Barrett, D.A., Thomas, E.L., Stott, C., Bell, J.D., O'Sullivan, S.E., Tan, G.D., 2016. Efficacy and safety of cannabidiol and tetrahydrocannabivarin on glycemic and lipid parameters in patients with type 2 diabetes: a randomized, double-blind, placebo-controlled, parallel group pilot study. Diabetes Care 39, 1777–1786. https://doi.org/10.2337/dc16-0650.

Johnson, J.R., Burnell-Nugent, M., Lossignol, D., Ganae-Motan, E.D., Potts, R., Fallon, M.T., 2009. Multicenter, double-blind, randomized, placebo-controlled, parallel-group study of the efficacy, safety, and tolerability of THC:CBD extract and THC extract in patients with intractable cancer-related pain. J. Pain Symptom Manag. 39 (2), 167–179. https://doi.org/10.1016/j.jpainsymman.2009.06.008.

Khodadadi, H., Salles, É.L., Jarrahi, A., Chibane, F., Costigliola, V., Yu, J.C., Vaibhav, K., Hess, D.C., Dhandapani, K.M., Baban, B., 2020. Cannabidiol modulates cytokine storm in acute respiratory distress syndrome induced by simulated viral infection

using synthetic RNA. Cannabis Cannabinoid Res 5, 197–201. https://doi.org/10.1089/can.2020.0043.

King, K.M., Myers, A.M., Soroka-Monzo, A.J., Tuma, R.F., Tallarida, R.J., Walker, E.A., Ward, S.J., 2017. Single and combined effects of Δ9-tetrahydrocannabinol and cannabidiol in a mouse model of chemotherapy-induced neuropathic pain. Br. J. Pharmacol. 174, 2832–2841. https://doi.org/10.1111/bph.13887.

Leas, E.C., Hendrickson, E.M., Nobles, A.L., Todd, R., Smith, D.M., Dredze, M., Ayers, J. W., 2020. Self-reported cannabidiol (CBD) use for conditions with proven therapies. JAMA Netw. open 3, e2020977. https://doi.org/10.1001/jamanetworkopen.2020.20977.

Lewis, M.A., Russo, E.B., Smith, K.M., 2018. Pharmacological foundations of cannabis chemovars. Planta Med. 84, 225–233. https://doi.org/10.1055/s-0043-122240.

Lavie-Ajayi, M., Shvartzman, P., 2019. Restored self: a phenomenological study of pain relief by cannabis. Pain Med. 20 (11), 2086–2093. https://doi.org/10.1093/pm/pny176. PMID: 30215782.

Mahabir, V.K., Merchant, J.J., Smith, C., Garibaldi, A., 2020. Medical cannabis use in the United States: a retrospective database study. J. Cannabis Res. 2 https://doi.org/10.1186/s42238-020-00038-w.

McGuire, P., Robson, P., Cubala, W., Vasile, D., Morrison, P., Barron, R., et al., 2018. Cannabidiol (CBD) as an adjunctive therapy in schizophrenia: a multicenter randomized controlled trial. Am. J. Psychiatr. 175 (3), 225–231. https://doi.org/10.1176/appi.ajp.2017.17030325.

Mechoulam, R., Ben-Shabat, S., 1999. From gan-zi-gun-nu to anandamide and 2-arach-idonoylglycerol: the ongoing story of cannabis. Nat. Prod. Rep. 16, 131–143. https://doi.org/10.1039/a703973e.

Minnesota Department of Health 2020. Medical Cannabis Programm Update. https://www.health.state.mn.us/people/cannabis/docs/about/quarupdates/oct2020.pdf [accessed May 5th 2021].

Naftali, T., Bar-Lev Schleider, L., Sklerovsky Benjaminov, F., Lish, I., Konikoff, F.M., Ringel, Y., 2019. Medical cannabis for inflammatory bowel disease: Real-life experience of mode of consumption and assessment of side-effects. Eur. J. Gastroenterol. Hepatol. 31, 1376–1381. https://doi.org/10.1097/MEG.0000000000001565.

Namdar, D., Voet, H., Ajjampura, V., Nadarajan, S., Mayzlish-Gati, E., Mazuz, M., Shalev, N., Koltai, H., 2019. Terpenoids and phytocannabinoids co-produced in cannabis sativa strains show specific interaction for ell cytotoxic activity. Molecules 24. https://doi.org/10.3390/molecules24173031.

National Academies of Sciences and Medicine (NASEM), 2017. The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research. The National Academies Press, Washington, DC. https://doi.org/10.17226/24625.

Nutt, D., Bazire, S., Phillips, L.D., Schlag, A.K., 2020. So near yet so far: why won't the UK prescribe medical cannabis? BMJ Open 10, e038687. https://doi.org/10.1136/bmjopen-2020-038687.

Nutt, D.J., Phillips, L.D., Barnes, M.P., Brander, B., Curran, H.V., Fayaz, A., Finn, D.P., Horsted, T., Moltke, J., Sakal, C., Sharon, H., O'Sullivan, S.E., Williams, T., Zorn, G., Schlag, A.K., 2021. A multicriteria decision analysis comparing pharmacotherapy for chronic neuropathic pain, including cannabinoids and cannabis-based medical products. Cannabis Cannabinoid Res. https://doi.org/10.1089/can.2020.0129. Online First.

O'Shaughnessy, W.B., 1843. On the preparations of the Indian hemp, or gunjah, (cannabis indica). Prov Med J Retrosp Med Sci 5 (123), 1–7.

O'Sullivan, S.E., Stevenson, C.W., Laviolette, S.R., 2020. Could cannabidiol Be a treatment for coronavirus disease-19-related anxiety disorders? Cannabis Cannabinoid Res. Online First 6 (1), 7–18. https://doi.org/10.1089/can.2020.0102.

Pamplona, F.A., da Silva, L.R., Coan, A.C., 2018. Potential clinical benefits of CBD-rich cannabis extracts over purified CBD in treatment-resistant epilepsy: Observational data meta-analysis. Front. Neurol. 9, 759. https://doi.org/10.3389/fneur.2018.00759.

Picardo, S., Kaplan, G.G., Sharkey, K.A., Seow, C.H., 2019. Insights into the role of cannabis in the management of inflammatory bowel disease. Therap. Adv. Gastroenterol. 12 https://doi.org/10.1177/1756284819870977.

Reiman, A., Welty, M., Solomon, P., 2017. Cannabis as a substitute for opioid-based pain medication: patient self-report. Cannabis Cannabinoid Res 2, 160–166. https://doi.org/10.1089/can.2017.0012.

Reynolds, J.R., 1890. On the therapeutical uses and toxic effects of Cannabis Indica. Lancet 135, 637–638. https://doi.org/10.1016/S0140-6736(02)18723-X.

Rock, E.M., Limebeer, C.L., Parker, L.A., 2018. Effect of cannabidiolic acid and Δ9-tetrahydrocannabinol on carrageenan-induced hyperalgesia and edema in a rodent model of inflammatory pain. Psychopharmacology (Berlin) 235, 3259–3271. https://doi.org/10.1007/s00213-018-5034-1.

Rose, J.E., Behm, F.M., 1994. Inhalation of vapor from black pepper extract reduces smoking withdrawal symptoms. Drug Alcohol Depend. 34, 225–229. https://doi.org/10.1016/0376-8716(94)90160-0.

Salles, É.L., Khodadadi, H., Jarrahi, A., Ahluwalia, M., Paffaro, V.A., Costigliola, V., Yu, J.C., Hess, D.C., Dhandapani, K.M., Baban, B., 2020. Cannabidiol (CBD) modulation of apelin in acute respiratory distress syndrome. J. Cell Mol. Med. 24, 12869–12872. https://doi.org/10.1111/jcmm.15883.

Samarut, É., Nixon, J., Kundap, U.P., Drapeau, P., Ellis, L.D., 2019. Single and synergistic effects of cannabidiol and δ-9-tetrahydrocannabinol on zebrafish models of neuro-hyperactivity. Front. Pharmacol. 10 https://doi.org/10.3389/fphar.2019.00226.

Santiago, M., Sachdev, S., Arnold, J.C., et al., 2019. Absence of entourage: terpenoids commonly found in Cannabis sativa do not modulate the functional activity of Δ9-THC at human CB1and CB2 receptors. bioRxiv 4 (3), 165–176, 2019;569079.

Schmidt-Wolf, G., Cremer-Schaeffer, P., 2019. Begleiterhebung zur Anwendung von Cannabisarzneimitteln in Deutschland – Zwischenauswertung. Bundesgesundheitsblatt - Gesundheitsforsch. - Gesundheitsschutz 62, 845–854. https://doi.org/10.1007/s00103-019-02968-0.

Schubert, D., Kepchia, D., Liang, Z., Dargusch, R., Goldberg, J., Maher, P., 2019. Efficacy of cannabinoids in a pre-clinical drug-screening platform for Alzheimer's disease. Mol. Neurobiol. 56, 7719–7730. https://doi.org/10.1007/s12035-019-1637-8.

Sexton, M., Cuttler, C., Finnell, J.S., Mischley, L.K., 2016. A cross-sectional survey of medical cannabis users: patterns of use and perceived efficacy. Cannabis Cannabinoid Res 1, 131–138. https://doi.org/10.1089/can.2016.0007.

Solowij, N., Broyd, S.J., Beale, C., Prick, J.A., Greenwood, L.M., Van Hell, H., Suo, C., Galettis, P., Pai, N., Fu, S., Croft, R.J., Martin, J.H., Yücel, M., 2018. Therapeutic effects of prolonged cannabidiol treatment on psychological symptoms and cognitive function in regular cannabis users: a pragmatic open-label clinical trial. Cannabis Cannabinoid Res 3, 21–34. https://doi.org/10.1089/can.2017.0043.

Stith, S.S., Vigil, J.M., Brockelman, F., Keeling, K., Hall, B., 2019. The association between cannabis product characteristics and symptom relief. Sci. Rep. 9 https://doi.org/10.1038/s41598-019-39462-1.

Stockings, E., Campbell, G., Hall, W.D., Nielsen, S., Zagic, D., Rahman, R., Murnion, B., Farrell, M., Weier, M., Degenhardt, L., 2018. Cannabis and cannabinoids for the treatment of people with chronic noncancer pain conditions: a systematic review and meta-analysis of controlled and observational studies. Pain 159, 1932–1954. https://doi.org/10.1097/j.pain.0000000000001293.

Takakuwa, K.M., Hergenrather, J.Y., Shofer, F.S., Schears, R.M., 2020. The impact of medical cannabis on intermittent and chronic opioid users with back pain: How cannabis diminished prescription opioid usage. Cannabis Cannabinoid Res 5, 263–270. https://doi.org/10.1089/can.2019.0039.

Ueberall, M.A., Essner, U., Mueller-Schwefe, G.H., 2019. Effectiveness and tolerability of THC:CBD oromucosal spray as add-on measure in patients with severe chronic pain: analysis of 12-week open-label real-world data provided by the German Pain e-Registry. J. Pain Res. 12, 1577–1604. https://doi.org/10.2147/JPR.S192174.

United Patients' Alliance (UPA) 2018. Patient Survey. https://www.upalliance.org [accessed May 1st 2020].

Wang, B., Kovalchuk, A., Li, D., Rodriguez-Juarez, R., Ilnytskyy, Y., Kovalchuk, I., Kovalchuk, O., 2020. In search of preventative strategies: novel high-CBD *cannabis sativa* extracts modulate ACE2 expression in COVID-19 gateway tissues. Aging (Albany. NY). https://doi.org/10.18632/aging.202225.

Ware, M.A., Adams, H., Guy, G.W., 2005. The medicinal use of cannabis in the UK: results of a nationwide survey. Int. J. Clin. Pract. 59, 291–295. https://doi.org/10.1111/j.1742-1241.2004.00271.x.

Ware, M.A., Wang, T., Shapiro, S., Collet, J.P., 2015. Cannabis for the management of pain: assessment of safety study (COMPASS). J. Pain 16, 1233–1242. https://doi.org/10.1016/j.jpain.2015.07.014.

Whiting, P.F., Wolff, R.F., Deshpande, S., Di Nisio, M., Duffy, S., Hernandez, A.V., Keurentjes, J.C., Lang, S., Misso, K., Ryder, S., Schmidlkofer, S., Westwood, M., Kleijnen, J., 2015. Cannabinoids for medical use: A systematic review and metaanalysis. JAMA - J. Am. Med. Assoc. 313, 2456–2473. https://doi.org/10.1001/jama.2015.6358.

Wiese, B., Wilson-Poe, A.R., 2018. Emerging evidence for cannabis' role in opioid use disorder. Cannabis Cannabinoid Res 3 (10), 179–189. https://doi.org/10.1089/can.2018.0022.

Wong, H., Cairns, B.E., 2019. Cannabidiol, cannabinol and their combinations act as peripheral analgesics in a rat model of myofascial pain. Arch. Oral Biol. 104, 33–39. https://doi.org/10.1016/j.archoralbio.2019.05.028.

Zafar, R., Schlag, A.K., Nutt, D., 2020. Ending the pain of children with severe epilepsy? An audit of the impact of medical cannabis in ten patients. Drug Sci. Policy Law. 6, 1–6.