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Medicinal Cannabis - Is there a Role in Psychiatric Disorders?

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Abstract

Objectives: There is an increase in lobbying for legalization or decriminalization of cannabis and cannabinoids in many countries. In some countries legal processes are already underway, as in New Zealand to permit use of cannabis for medicinal purposes, despite the paucity of research to justify such policy decisions. Public approval drives such policy moves and often without the accompanying scientific data that are normally essential to justify the introduction of a new medication in the market. Amidst this rush and media publicity, there is a need to pause and gauge the potential impact of such policy changes especially with regard to patients with mental illness, including schizophrenia, mood, and anxiety disorders.

Methods: A selective literature review was conducted to examine peer reviewed publications on medicinal usage of cannabis in psychiatry.

Results: The efficacy and safety of cannabis-based medicines for treatment or alleviation of psychiatric disorders has been examined in the scientific literature recently. Data to support the beneficial effects of cannabis use in psychiatric populations are limited and conflicting. Potential harms to people with psychotic and mood disorders have been increasingly documented. Human CBD studies for epilepsy and psychiatric disorders reported CBD-induced drug-drug interactions, hepatic abnormalities, diarrhea, fatigue, vomiting, and somnolence. This paper reviews current prevailing evidence for the role and validity of medicinal cannabis/cannabinoids specific to the psychiatric population with the intent of raising awareness of physicians to decide for themselves whether medicinal cannabis is panacea, scourge, or both.

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Introduction

There is a significant growth of interest in medicinal cannabinoids for mental health applications [1]. There is a significant financial interest in this sector. Biotechnology companies are researching to replace cannabis plants with genetically enhanced microorganisms to produce Tetrahydrocannabinol (THC), Cannabidiol (CBD) and other cannabinoids with claims of medicinal usefulness [2]. Proliferation in available CBD products with potential medical application are expected. For the purposes of this review, medicinal cannabis includes all plant-derived and synthetic derivatives aimed for medical purposes, including treatment of mental disorders. Recent scientific evidence ascribes anxiolytic, neuroprotective, antioxidant, anti-inflammatory, antidepressant, anti-psychotic and hypnotic pharmacological actions to CBD [1-8]. Not all these indications are supported by robust scientific data and some assertions are influenced by strong market forces.

Objectives

We examine the current claims in this regard in the context of New Zealand where the changes have been recent and could prove useful for other countries considering permitting use of cannabis based products for medical use.

Methods

We conducted a selective literature review of peer reviewed publications in Pubmed by using key words cannabis, medicinal, legalisation and decriminalisation. Identified abstracts were then screened and additional references were identified from the papers reviewed. We also examined government publications from New Zealand for local policy issues.

Results

Medicinal Cannabis Scheme, New Zealand

In the context of New Zealand, the Medicinal Cannabis Scheme (MCS) came into effect on 1 April 2020 with Misuse of Drugs (Medicinal Cannabis) Regulations 2019. The aim of this scheme was to improve access to quality medicinal cannabis products by increasing supply of products and improving access for patients. The Medicinal Cannabis Agency (MCA) became operational to administer the regulatory functions of the Scheme that includes licensing, product assessments and compliance. The transition period for the Agency from 1 April to 30 September 2020 allowed for a continued supply of products that were available before 1 April 2020. From 1 October 2020, no supplier is allowed to distribute any cannabis based products in New Zealand which do not meet the quality standard. Through this legislation medicinal cannabis products became prescription only medicine available to patients from a doctor [9]. Long before the enactment of the MCS, the role of cannabis, including herbal, as a medicinal agent was subject to vigorous debate in the scientific media [10-14]. Medicinal use of cannabis was legalized despite only moderate-quality evidence to support its use for the treatment of chronic pain and spasticity, and low-quality evidence to support use of cannabinoids for nausea and vomiting due to chemotherapy, weight gain in HIV infection, sleep disorders and Tourette's syndrome. Movement to widen the scope of cannabis has gained momentum and is being driven by lobbying from patients and their families, and pro-recreational cannabis law reform organisations often with vested financial interest [13]. Almost immediately post legislation the Associate Minister of Health, Honourable Peter Dunne granted a one off approval of a cannabis-derived product Elixinol™ for the treatment of a coma patient suffering from status epilepticus "on compassionate grounds", despite the lack of clinical evidence about the efficacy of the product. Such arbitrary decisions by politicians always raises the possibility of repetition and growing pressures from the public.

Public interest in the medicinal usage of cannabis is also reported by studies from New Zealand. A study of 134 patients recruited from General Practices across North Island, New Zealand found 71% of those who believed cannabis to be beneficial, perceived it useful for pain relief [15]. While 92% participants stated they were comfortable in discussing medicinal cannabis use with GPs and specialists, less than 10% had done this. Pledger et al., (2016) found respondents reported medicinal use of cannabis for conditions that were typically hard to manage including pain, anxiety/nerves and depression [16]. Globally, since the FDA approval of CBD preparation (98% cannabidiol) for intractable epilepsy and the emerging evidence from ongoing research, unapproved CBD products appearing in the market without appropriate standardization of CBD potency, presence of other constituents and with unproven claims of health effects. It is likely that off-label prescriptions will increase leading to potential harmful consequences. Possible factors contributing to CBD adverse events are CBD potency, route of administration (vaporized, transdermal, oral), concurrent licit and illicit drug use, and drug-drug interactions [17]. It is in this context of a new legislation, growing public interest in diversifying scope for prescribing cannabis and financial interests of the cannabis industry that we present our summary of the literature on role of Cannabinoids (CBD) in psychiatric disorders. We focus on psychiatric population because psychiatric patients are perhaps the largest group of people using cannabis already and may be at risk of exploitation by financial motives as has happened with the tobacco industry. We use the term cannabinoids to include any refined constituent of the cannabis plant i.e. THC or CBD. To this effect we first review basic pharmacology of cannabinoids and then explore the evidence in the treatment of various psychiatric disorder.

Basic Pharmacology of Cannabinoids

Cannabinoids include three groups of chemicals with medicinal properties:-

Endocannabinoids: Occur naturally in the human body having a role to play in ensuring homeostasis, i.e. maintaining a stable internal environment despite fluctuations in the external environment. They act on CB1 + CB2 receptors influencing physiological systems and play a pivotal role in Central Nervous System (CNS) development, synaptic plasticity, motor control, memory, cognition, stress, emotional responses, reward and motivated behaviour, appetite, pain, development and homeostasis [18].

Phytocannabinoids: This group is perhaps the most widely researched among cannabinoids and includes Δ9-Tetrahydrocannabinol (THC) and CBD. THC is the primary constituent of cannabis that causes the "high" whereas CBD is not intoxicating at typical doses [13]. Phytocannabinoids mimic the action of the natural endocannabinoids. THC acts on CB1 + CB2 receptors influencing neuronal signalling processes of the Endocannabinoid System (ECS), and interfering with homeostatic balance [19]. CBD has a low affinity for the receptors, acts on the immune system, blocks the reuptake of anandamide and inhibits its enzymatic hydrolysis [20].

Synthetic cannabinoids: Dronabinol and nabilone are synthetic in origin, mimic the effects of THC, and have licenced indication for chemotherapy-induced nausea and vomiting. Dronabinol has an identical structure to THC, while nabilone has a related structure and is more potent than dronabinol, requiring lower doses to achieve clinical efficacy [21].

Cannabinoids pharmacokinetics: Cannabinoids administered via inhalation or intravenously exhibit similar pharmacokinetics. Peak plasma concentrations of CBD, like THC, are attained (within 3-10 min) and maximum concentrations are higher relative to oral ingestion. The bioavailability of oral CBD ranges between 11 and 13%, compared to 11 to 45% via inhalation. THC and CBD are both highly lipophilic and have poor oral bioavailability (as low as 6%) [22,23].

Potential drug interactions of CBD: Comorbidities with physical and other psychiatric conditions is common among people with psychiatric conditions who often take psychiatric and non- psychiatric medication. Drug interactions are therefore important while considering CBD use. CBD is a potent inhibitor of CYP-2D6 and CYP-3A4, and can increase levels of drugs metabolised by these isoenzymes including macrolides, calcium channel blockers, benzodiazepines, cyclosporine, sildenafil (and other PDE5 inhibitors), antihistamines, haloperidol, antiretrovirals, and some statins (atorvastatin and simvastatin, but not pravastatin or rosuvastatin). CYP2D6 metabolizes many antidepressants, so CBD may increase serum concentrations of SSRIs, tricyclic antidepressants, antipsychotics, beta blockers and opioids (including codeine and oxycodone). CBD also acts as a substrate of CYP 3A4 and CYP2C19. Ketoconazole shown to increase CBD levels by two-fold [23,24].

Cannabinoids in subgroups of psychiatric disorders

As the popularity of cannabinoids increase people with a range of psychiatric conditions may wish to explore their usefulness. We present below what is reported in the literature in this regard.

Cannabinoids in cannabis use disorders (CUD)

CBD agonist activities on 5-HT1A receptors may contribute to its anti-craving effects, reducing relapses by regulating the drug reward system, anxiety symptoms and improving stress management. CBD also regulates the glutamatergic signalling via the modulation of the serotoninergic and the endocannabinoid systems which may serve a role in treating addictive behaviour [23], since a dysregulation of glutamatergic transmission has been widely related to both drug-seeking behaviour and relapse occurrence [7]. THC-based medicine (nabiximols, dronabinol) have been used as an adjunct in the treatment of CUD. Allsop et al. (2014) (n= 51) investigated the effects of nabiximols versus placebo and cognitive behavioural therapy. Both cohorts had decrease in cannabis use, number of cannabis-related problems, and severity of cannabis dependence but the inter group differences were not significant [25]. Several trials with smaller sample sizes showed mixed results with either nabiximols not influencing cannabis craving to reduction in cannabis use, withdrawal, and craving symptoms over time. Nabiximols was associated with a greater reduction in cannabis craving symptoms when compared with placebo [6]. Current data does not offer strong evidence for the use of cannabinoids in the treatment of CUD like we have seen the role of methadone in the management of opiate use disorders [26].

Cannabinoids in psychosis /schizophrenia

The effects of CBD have been studied in patients in both early and later stages of psychotic disorders. Majority of the findings are, however, based on small studies or anecdotal reports. Good quality data is lacking to support widespread usage of CBD in people with psychosis or schizophrenia. A double-blind, randomized clinical trial of CBD *vs.* amisulpride in acute schizophrenia found both treatments were safe and yielded significant clinical improvement with better side effect profile with the former [27]. CBD increased serum anandamide concentrations as CBD moderately inhibits degradation of the anandamide. Another study reported a significant increase in anandamide levels after CBD treatment that was associated with decrease of total PANSS score [28] and inverse association between elevated anandamide levels in cerebrospinal fluid and psychotic symptoms in antipsychotic-naïve patients [28]. A small study of 7 patients with psychosis with CBD-rich found medicinal cannabis did not affect psychosis- or dependence-related symptomatology [29]. A case report of a 57-year-old woman with treatment-resistant schizophrenia, for 21 years treated with CBD 500 (increased to750mg) twice daily adjunctive to clozapine (275 mg/day) and lamotrigine (225 mg/day), reported Improvement of symptomatology and the patient fulfilled remission criteria [30].

Cannabinoids in bipolar disorder (BPD)

Cannabis use is markedly more prevalent among those with BPD. Associations between cannabis use and negative outcomes in BPD such as worsened affective episodes, psychotic symptoms, rapid cycling, suicide attempts, decreased long-term remission, poorer global functioning, and increased disability imply that caution is warranted among cannabis users with BPD [31]. Endocannabinoid system is implicated in the bipolar spectrum disorders (BPD) but currently no clinical trial have assessed cannabinoids in maintaining euthymia, or as a treatment of hypo mania or depression [32]. Only cross-sectional studies have looked at the relation of cannabinoids and bipolar disorder but their findings are inconsistent [32]. In a case report two BPD patients presenting with mania, received adjunctive CBD (titrated to 1200mg per day) after receiving placebo for an initial five-day period, then replaced by placebo for five days. While the first patient showed symptom improvement with olanzapine plus CBD, she showed no additional improvement with CBD monotherapy. The second patient had no symptom improvement with any dose of CBD during the trial [7]. With such limited evidence it is premature to recommend CBD for the treatment of BPD.

Cannabinoids in anxiety disorders

The Endocannabinoid System (ECS) has been implicated in anxiety and mood due to its action on the CB1 receptors which in turn modulates GABAergic and glutamatergic transmission, influences the HPA axis, immune system activation, and neuroplastic mechanisms [7]. It has been suggested at least in the short term CB may have anxiolytic effects in experimental settings designed to induce stress/anxiety [32]. Applicability of such findings in the clinical setting remains limited. It is however widely known people with anxiety frequently seek cannabis for supposed treatment [30]. Some neuroimaging studies examining cerebral blood flow have reported beneficial effects of CBD among individuals diagnosed with social anxiety [7]. Evidence for CBD in GAD is limited and available results are inconclusive

about any claimed benefit in long-term anxiety symptoms [7]. We however don't know yet whether CBD is more effective or safer than the current alternatives such as SSRIs and SNRI in the treatment of anxiety disorders.

Cannabinoids in post traumatic stress disorder (PTSD)

Disruption to the ECS mechanisms caused by high concentrations of endocannabinoid receptors in the prefrontal cortex, amygdala and hippocampus, impairs fear acquisition and extinction [7]. This mechanism has been postulated as basis for use of CBD in the treatment of PTSD. Patients with PTSD often used cannabis to cope with sleep disturbances although over time they report significantly poorer sleep quality and physical health [33]. Most data suggests recreational cannabis users have a higher likelihood of presenting with PTSD symptoms, heightened negative affect, and showing improvements following cannabis abstinence [4]. Other studies either show mixed support for potential harms and therapeutic benefits, mostly involving sleep-related outcomes from cannabis use on psychiatric outcomes in PTSD [4]. A small case series (n= 11 adult patients at an outpatient psychiatry clinic) found administration of oral CBD added to routine psychiatric care was associated with PTSD symptom reduction especially offering relief in a subset of patients who reported frequent nightmares [34]. In another case series that used both THC and CBD in the treatment of PTSD modest improvement in anxiety and sleep [35] was reported. More studies are needed to develop a better understanding of the neurobiological mechanisms of CBD and examining the efficacy of CBD for PTSD.

Cannabinoids in depression

The use of cannabis/cannabinoids in depression is understandable in terms of the early and transient relief of some depressive symptoms which could contribute to its addictive potential [36]. Long-term cannabis use on the other hand negatively impacts on the course of depressive disorders especially in heavy cannabis users compared to light-users and nonusers. A cross-sectional anonymous online survey (n= 1429) found over 50% of respondents used medicinal cannabis specifically for depression [36], although the most frequently reported conditions for which they used cannabis were pain (61.2%), anxiety (58.1%), and headache/migraine (35.5%), nausea (27.4%), and muscle spasticity (18.4%). The study cautioned against using cannabis without physician supervision and for conditions for which there is no formal research to support the use of cannabis (e.g., depression and anxiety) [36].

Cannabinoids in dementia

Use of cannabinoids in dementia has gained popularity recently but quality data is lacking. In one Systematic Review (SR) of cannabinoids in Alzheimer's disease 6,902 papers were reviewed but only 9 were eligible. The included studies had explored THC (n= 3), dronabinol (n= 5), or nabilone (n= 1) and concluded cannabinoids were well-tolerated, with an overall trial completion rate of 93% (193/205). Treatment efficacy was associated with baseline dementia severity and dose, but not dementia subtype, age, or sex. The overall study quality was rated as low [37]. Another SR (n= twelve studies) examined the safety and effectiveness of cannabinoids in the treatment of neuropsychiatric symptoms in dementia found studies varied significantly with respect to study design (50% Randomized Controlled Trials (RCTs) or the type of intervention [dronabinol (33%), nabilone (25%) or THC; (42%)] or outcome measures. The highest-quality trial found no significant improvement in symptoms between treatment arms [38]. A further SR [39] found some evidence based on RCTs to support the usefulness of nabilone in the management of agitation in dementia, but no convincing evidence for THC and no role of cannabinoids for the treatment of cognitive decline in dementia. It is too early to suggest cannabinoids have any beneficial effect on dementia symptoms or their progression [39].

Discussion & conclusion

In essence it is currently premature to recommend cannabinoid-based interventions in the psychiatric settings. Case studies suggest that medicinal cannabis may have beneficial role for improving sleep and post-traumatic stress disorder, however evidence is currently weak. Preliminary research findings indicate no benefit for depression from THC [7]. Some studies report CBD may be effective to alleviate positive, negative, and cognitive symptoms in schizophrenia, as well as craving and withdrawal in substance use disorders. Variations in study design, patient population, and use of concomitant medication make it challenging to identify subgroups where CBD may benefit. In addition, CBD doses and administration varied between studies and the source of CBD were not specified (i.e., synthetic or cannabis extracted), which may have different efficacy.

Despite such limited data pressures on doctors to prescribe cannabis for non licensed conditions is likely to increase. Doctors will need to balance such pressures against the development of a strictly regulated system consisting of overly bureaucratic systems which could lead to higher healthcare costs, barriers to access and overburdening of the health system versus ensuring patient safety and treatment efficacy, and the need to distance the medicinal cannabis industry from regulatory design decisions [40]. Forces in both directions would be powerful and basing practice on solid evidence may be the only way forward. Until good quality data becomes available about the benefits and harm associated with using cannabis for medicinal purposes and on prescription, doctors will need to exercise extreme caution and be mindful that most cannabis-based products will sit outside of the safety net of prescribing lawfully and under indemnity [41]. We reiterate the caution by Rychert et al., (2019) only a pharmaceutical grade product should be accepted as a medicine and that "Cannabis" is not a single entity [42].

Interventional studies with purified CBD are warranted, with a call to target-engagement proof-of-principle studies using the research domain criteria framework [43]. Larger-scale, placebo controlled, clinical studies are needed as well to investigate the effects of CBD as an adjunct to psychological therapy [28] in both acute and chronic illnesses, special categories, as well as to exclude any possible abuse liability [5]. Clinical prescriptive consideration involves caution in the use of high-THC formulations, avoidance in youth, and in people with anxiety or psychotic disorders), gradual titration, regular assessment, and caution in cardiovascular and respiratory disorders, pregnancy and breast-feeding [7].

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