



Review

Cannabidiol in medical marijuana: Research vistas and potential opportunities



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ABSTRACT

The high and increasing prevalence of medical marijuana consumption in the general population invites the need for quality evidence regarding its safety and efficacy. Herein, we synthesize extant literature pertaining to the phytocannabinoid cannabidiol (CBD) and its brain effects. The principle phytocannabinoid Δ^9 -tetrahydrocannabinol (Δ^9 -THC) and CBD are the major pharmacologically active cannabinoids. The effect of CBD on brain systems as well as on phenomenological measures (e.g. cognitive function) are distinct and in many cases opposite to that of Δ^9 -THC. Cannabidiol is without euphoriant properties, and exerts antipsychotic, anxiolytic, anti-seizure, as well as anti-inflammatory properties. It is essential to parcellate phytocannabinoids into their constituent moieties as the most abundant cannabinoid have differential effects on physiologic systems in psychopathology measures. Disparate findings and reports related to effects of cannabis consumption reflect differential relative concentration of Δ^9 -THC and CBD. Existing literature, notwithstanding its deficiencies, provides empirical support for the hypothesis that CBD may exert beneficial effects on brain effector systems/substrates subserving domain-based phenomenology. Interventional studies with purified CBD are warranted with a call to target-engagement proof-of-principle studies using the research domain criteria (RDoC) framework.

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1. Introduction

It is estimated that approximately 180 million people between the ages of 18–65 have self-administered marijuana at least once in their lifetime globally [1]. According to the Global Burden of Disease Study, it was estimated that approximately 13 million people worldwide are dependent on cannabis [2]. It has also been reported that the rates of cannabis consumption in the general population is increasing, particularly amongst younger populations (i.e. high school students) [3]. The anticipated legalization of marijuana in various countries and jurisdictions (e.g. USA, Canada) in 2017, with the accompanied commercial interest in the sale of cannabinoid-containing products (i.e. medical marijuana), is predicted to further increase cannabis utilization, inviting the need for rigorous safety and efficacy data.

The overarching aim of this article is to provide healthcare providers and other stakeholders with pragmatic data-driven decision support regarding the pharmacology and putative clinical applications of CBD. We have specifically chosen three of the most common mental health complaints wherein patients seek out advice related to the use of medical marijuana as a treatment (i.e., anxiety, depression, and sleep) [4]. We delimit our focus to CBD, an active moiety in medical marijuana; recent systematic reviews and meta-analyses provide replicable and convergent evidence of the hazardous effects of Δ^9 -THC [5,6].

2. Methods

This is a narrative, non-systematic review of pre-clinical and clinical studies. An electronic literature search was conducted using the following databases: PubMed, PsychInfo, and Scopus from inception to November 2016. The search term *cannabidiol* was cross-referenced with the terms *anxiety*, *depression*, *sleep*, *cannabis*, and *medical marijuana*. We delimited our search to articles written in English that were published within the past ten years. Pharmacological, molecular, and physiologic studies evaluating the effects of CBD on neurobiological substrates subserving anxiety, mood, and sleep complaints were included. Where available, we also included human interventional studies that investigated the efficacy of CBD on anxiety, mood, and sleep symptoms. Bibliographies were also manually searched for additional citations that were relevant to the overarching aim of this paper.

2.1. What are the pharmacologically active constituents of medical marijuana?

Cannabinoid is the generic term for the active constituents produced by strains of the cannabis plant (e.g. *C. sativa*, *C. indica*). Colloquially, cannabis is often used interchangeably with marijuana, with inhalation being the most common route of administration (other routes include oils, tinctures, oral-mucosal spray, and edibles). The two major constituents of cannabis are the phytocannabinoids: Δ^9 -tetrahydrocannabinol (Δ^9 -THC) and cannabidiol (CBD). Δ^9 -Tetrahydrocannabinol is the principle psychoactive moiety that induces euphoria, altered sensory perception and relaxation, also known as the “high” that is enjoyed by many users; the potential for misuse, withdrawal, and adverse psychological effects (e.g., psychosis, cognitive impairment, amotivation syndrome and anxiogenesis) has been well characterized [5]. During the past two decades, the concentration of Δ^9 -THC in cannabis has considerably increased approaching 15–20% in some preparations [6].

Table 1
Putative Receptor Targets of Cannabidiol [45].

Receptor	CBD activity
CB ₁	Noncompetitive antagonist
CB ₂	Inverse agonist
GPR55	Antagonist
PPAR- γ	Agonist
TRPM8	Antagonist
α_1 , α_3 glycine	Agonist
5-HT _{1a}	Agonist
TRPV1, TRPV2 channels	Agonist
TRPA1	Antagonist

CB₁ = cannabinoid type 1 receptor; CB₂ =cannabinoid type 2 receptor; GPR55 =G protein-coupled receptor 55; PPAR- γ =nuclear peroxisome proliferator-activated receptor γ ; TRPM8=transient receptor potential of the melastatin type 8; 5-HT_{1a} = serotonin receptor; TRPV1 = transient receptor potential of vanilloid type 1; TRPV2 =transient receptor potential of vanilloid type 2; TRPA1 = transient receptor potential of ankyrin type 1.

2.2. What is the pharmacology of THC and CBD?

Cannabidiol exerts complex actions at multiple receptors within the endocannabinoid system (ECS) (Table 1). The ECS consists of cannabinoid receptors, endogenous ligands and enzymes within the brain and immune system [7]. The two principal cannabinoid receptors are cannabinoid receptor type-1 (CB₁) and cannabinoid receptor type-2 (CB₂), both distributed throughout the brain with greater expression in the neocortex, basal ganglia, and hippocampus [8]. Cannabinoid receptor type-2 is also identified in the hematopoietic system [8,9]. The CB₁/CB₂ receptor systems have a mechanistic role in memory, appetite, and stress response [10]. Moreover, CB₁/CB₂ are intrinsic to neurobiological substrates subserving reward and reinforcement [11].

Cannabidiol acts as a non-competitive antagonist at CB₁ receptors and an inverse agonist at CB₂ receptors [12]. Cannabidiol inhibits the reuptake and enzymatic degradation of the endogenous cannabinoid anandamide (*N*-arachidonylethanolamine or AEA) [13]. Anandamide has well-established effects on neuronal/synaptic remodelling and pruning. The foregoing effects of CBD are in contradistinction to Δ^9 -THC, which is known to result in relative depletion of AEA; moreover, the depletion of AEA is thought to mediate the psychotomimetic effects of Δ^9 -THC [14]. Cannabidiol also exerts agonistic activity at the 5-HT_{1a} receptors, an effect that is hypothesized to mediate potential antidepressant, anxiolytic and procognitive effects [15].

Results from naturalistic and mechanistic studies indicate that CBD modulates neural substrates subserving reward behaviours [21,22]. For example, inhalational CBD is demonstrated to significantly reduce cigarette consumption amongst chronic smokers [16]. Further proof-of-concept evidence rectifying CB₁ receptor antagonism as critical to CBD’s reward modulating effects is provided by observations that rimonabant, a CB₁ receptor antagonist, also significantly reduces cigarette consumption [16].

2.3. What are the effects of Δ^9 -THC and CBD on brain function?

Extant literature amply documents the deleterious effects of chronic marijuana usage on human brain function including decreased cognitive function (e.g. executive function, learning and memory, attention), amotivation syndrome, as well as the induction of psychosis in “at-risk” populations [4–7]. For example, longitudinal population-based studies report an approximate two-fold increase in the risk of psychotic illness in cannabis-using adolescents [8]. In contradistinction to the hazardous effects of Δ^9 -THC on the central nervous system, human interventional studies with CBD have not identified any significant amplification or engendering psychopathological measures [17,18]. In contradistinction,

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