Essay title: Cannabinoid compounds are associated with an increased risk of psychiatric disorders, but they also have a therapeutic potential in the mental health field. Discuss these two aspects, with focus on the mechanism of action of cannabinoids.

Abstract

Cannabis is a plant mainly containing delta-9-tetrahydrocannabinol and cannabidiol. It is the most used illegal drug worldwide. These chemicals act by binding onto cannabinoid receptors resulting in the inebriated effects shown after consumption. Overtime, we have seen a noticeable increase in the chemical composition of cannabis as well as increased cases of psychotic symptoms and mental disorders. We have also seen the therapeutic potential cannabis can have when regulated and used correctly. This essay attempts to draw links and expand upon these properties as well as justify certain uses of cannabis by isolating and using certain chemicals. Furthermore, this essay addresses the consequences of increasing delta-9-tetrahydrocannabinol and decreasing cannabidiol in cannabis over a long period of time and explain why this is leading to the rise of addiction and the worsening of psychiatric conditions.

Cannabis is a complex plant composed of numerous chemicals known as cannabinoids that bring about physical, mental, and cognitive changes when taken into the body [1]. It has become the most widely used illegal drug in the world [1]. Cannabinoids are classified into naturally occurring phytocannabinoids, endocannabinoids which are produced in the body and synthetic cannabinoids [2]. The two main phytocannabinoids found in cannabis are delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) [2]. They can be taken into the body through various methods such as smoking, ingestion and with sprays sublingually [2]. These modes of administration differ in their onset of action as well as their potencies which diversifies the options available for cannabis users, often resulting in an increased selection with higher dosages [2]. Over the last 3 decades we have seen a rise of incidence in cannabis users followed by an exponential increase in THC found in these plants. The increase from 2% in the 1980s to upwards of 28% of THC in these plants sprouts the question of whether this increase is beneficial or whether this is exacerbating the risk of addiction and the emergence of psychiatric disorders [3]. With this in mind, cannabis has the potential to remain as a potential therapeutic benefit to a range of mental illnesses and with strict regulation it can be heralded as an alternative treatment option. Despite the dramatic increase of research into endocannabinoids in recent years researchers are yet to fully understand the complete functions it provides. As a result, this essay will mainly address the effects phytocannabinoids exert onto the body while mentioning endocannabinoids where possible. This essay will be introducing the cannabinoid receptors found in the body before expanding on their mode of action. I will be explaining the roles that CBD and THC play in the endocannabinoid system before addressing the risks that cannabinoids can cause in psychiatric disorders. Finally, I will be reinforcing the potential benefits cannabinoids can bring in improving certain mental health disorders.

Cannabinoids exert their action by selectively binding to specific receptors located within our body. Knowledge of these receptors and their effects are paramount to begin drawing links between their activity and the progression of psychiatric disorders. Cannabinoids work by stimulating cannabinoid receptor type 1 (CB1) and type 2 (CB2) [4]. These receptors are located within the endocannabinoid system which are composed of an intricate network of neurotransmitters and receptors spread across the body [4]. This system plays a vital role in homeostasis where it acts to mediate bodily processes such as pain, memory, and appetite

[4]. Cannabinoid receptors are classified as G-protein coupled receptors (GPCR) which function to signal transduction pathways [4]. CB1 is the most abundant GPCR in the brain and can be found in regions such as the basal ganglia and the limbic system [4]. Studies have shown CB1 receptor's involvement in mediating psychoactivity [1]. In contrast, CB2 receptors are mainly expressed in immune cells and the gastrointestinal system, and the same study suggested CB2 receptors are not involved in mediating psychoactivity but have a role in proliferation and survival of neurones [1]. At a neuronal level, CB1 receptors are located on the terminals of central and peripheral neurons where they exert inhibitory effects by mediating the release of excitatory and inhibitory neurotransmitters such as dopamine, gamma-aminobutyric acid (GABA) and glutamate among a few others [1]. To supplement the current information on cannabinoid receptors it is imperative we address the effects of THC and CBD on these receptors, which would aid in distinguishing the two chemicals as well as finding any similarities between them.

To better explain the changes that occur within the body the action of phytocannabinoids should be expanded upon. THC is found to be a partial agonist to CB1 and figure 1 provides a visual aid on what occurs during this interaction [1]. Once THC binds onto the receptor on the presynaptic terminal it leads to an increased potassium conductance and decreased calcium conductance [1]. This results in the inhibition of the release of neurotransmitters such as dopamine, GABA and glutamate which is depicted by the thinner red line on figure 1. In addition, THC is also a partial agonist to CB2 receptors causing anti-inflammatory effects and pain relief [1]. Since these neurotransmitters are released in numerous brain regions and are involved in several essential processes, disruption and dysregulation of their release can lead to deleterious effects. Some of the effects shown after cannabis consumption are dependent on the specific region of the brain affected; increased appetite can be attributed to changes in the hypothalamus whereas impairment of short-term memory is caused by changes in the hippocampus [2]. The exact molecular mechanism of CBD is not fully understood as studies have shown its low affinity for CB1 and

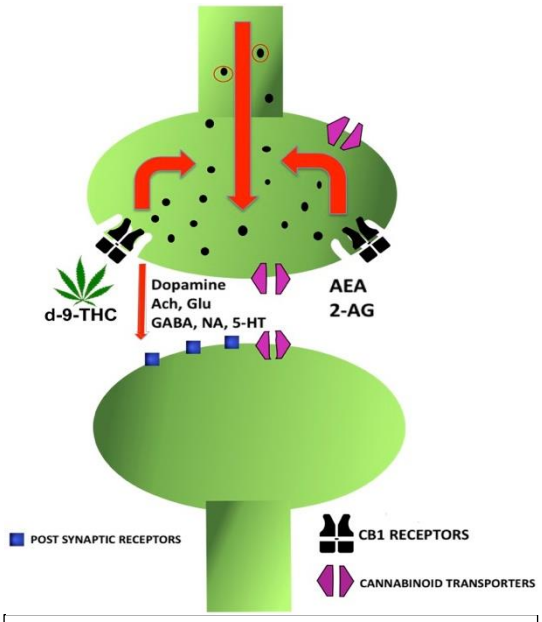
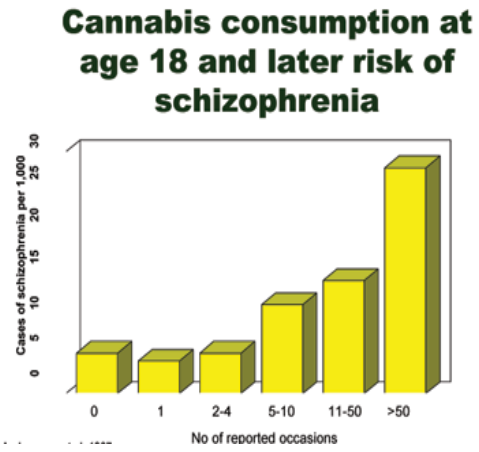


Figure 1: Labelled diagram illustrating interaction of THC and CB1 on presynaptic terminal [1]

CB2 receptors [5]. It was suggested that CBD exerts its action through 2 methods: acting upon anandamide or the transient receptor potential vanilloid type 1 (TRPV1) [5]. Anandamide, an endogenous cannabinoid that acts on CB1 and CB2 is degraded by fatty acid amide hydrolase [5]. CBD works to either inhibit this enzyme or the transporter for anandamide leading to an increased level [5]. Furthermore, CBD is found to be a full agonist of TRPV1 alongside anandamide which are thought to be involved in sensing changes in the internal body temperature and inflammatory hyperalgesia [5]. THC and CBD share similar properties such that they both can exert effects such as an anticonvulsant, anti-inflammatory and as a muscle relaxant [1]. However, they also exhibit opposing effects, and this can be shown since THC is psychoactive whereas CBD is considered not to exhibit psychotropic effects [1]. In fact, CBD exerts antipsychotic activity and is thought to be neuroprotective [1]. With a better understanding of how these chemicals act to release their effects and a better recognition of their differences we can begin to address the consequences that have arisen from gradually increasing the THC:CBD ratio overtime.

We have seen a noticeable rise of THC in cannabis over the last 30 years and this is followed by a subsequent decline in CBD. This is quantified once you look at the THC:CBD ratio in cannabis. The ratio was found to have increased steeply from 14 in 1995 to 80 in 2014 [3]. This becomes a problematic issue as studies have portrayed a dose response with an increased likelihood of addiction [3]. This results in individuals seeking cannabis with a higher potency of THC or can result in an increased frequency of smoking. The emergence of THC containing products such as smokable dabs or ingestible edibles, with concentrations up to 95% only worsens this predicament as no evidence is shown to assess the safety and benefit of THC concentrations that high [6]. With increased and chronic usage of cannabis we begin to see structural changes that occurs in the brain due to the disruption that cannabinoids can cause in neurotransmitter release [6]. The rise of addiction in cannabis users only reinforces the severity of the increase in THC as withdrawal symptoms such as increased anger and irritability were not identified when THC concentrations were much lower [6]. Despite studies emphasising the antipsychotic properties of CBD as well as



its opposing action to THC, it continues to decrease which results in a vicious cycle forming [6]. With the increased availability of cannabis, we see this cycle of increased smoking with reduced CBD concentration forming which further exacerbates the risk of mental disorders [6]. These can include depression, anxiety and a poorer memory which could have been alleviated had there been an increase in CBD [6]. Taking this into account, it is important to recognise the presentation of psychiatric disorders and why their risk elevates due to this rise in THC.

There have been implications that suggest THC's involvement in the development of psychotic symptoms and psychiatric disorders. One that has been extensively researched is schizophrenia and its present risk with the use of cannabis [7]. Numerous peer review papers have studied the effects of THC in this regard and the consensus was found to be a positive correlation between cannabis use and the emergence of psychotic symptoms and schizophrenia in a dose-dependent manner [7]. Figure 2 illustrates this link between the frequency of use and the onset of schizophrenia even more, emphasising the increase of risk from 4% at baseline to almost 30% at more than 50 reported occasions [8]. We can attempt to explain this emergence by looking at the involvement of cannabinoid receptors with neurotransmitter activity. Looking at the dopaminergic pathways, we can attribute certain symptoms of psychosis to the hyperactivity of this pathway [7]. There have been inclinations on the coexpression of CB1 and dopamine D2 receptors in numerous brain regions resulting in increased mesolimbic dopaminergic activity upon stimulation of CB1 receptors [7]. This is achieved through the cannabinoids' activation of impulses onto these dopaminergic neurones thereby inducing dopamine release into the striatum [7]. Upon comparison, schizophrenic patients also exhibit induced dopamine release allowing a theoretical link to be drawn between this exposure and the exacerbation of the disease upon cannabis consumption [7]. To add onto this, CB1 activation in the prefrontal cortex (PFC) has been linked with modulation of dopaminergic activity in this region [7]. With the suppression of GABA and dopamine release, the prefrontal cortex may be non-selectively activated resulting in disruption to normal signal processing [7]. It is important to note that the PFC operates under strict levels of neurotransmitter release and fluctuations to this level can lead to cognitive impairments, some of which are exacerbated in schizophrenic patients

Figure 2: Bar chart portraying the number of reported occasions of smoking and the cases of schizophrenia seen [8]

which further reinforces the connection between the drug and the worsening of the disorder [7]. The suppression of GABA in other regions such as the hippocampus disrupts other cognitive processes in the brain. The major consequence is the desynchronisation of pyramidal cells through disinhibition which would interfere with the cell's role in memory consolidation and perceptual processes [7]. When considering other explanations for the psychotomimetic effects of THC we can include the disruption of glutamate release as another possible cause [7]. Numerous studies established the presence of glutamate transmission in regions such as the hippocampus and the PFC [7]. Modulation of glutamate release by THC reduces NMDA receptor activity in those brain regions which is possibly causing the symptoms shown in psychosis and schizophrenia [7]. With the current data presented, one must be critical when assessing the risks and benefits of a certain substance. As a result, factoring in the potential therapeutic benefits of CBD is imperative to draw a reasonable conclusion on the exact uses of cannabis.

Throughout this essay we have touched upon certain properties that CBD produces. With the present ideas in mind, it is vital to expand upon them and provide insights to what benefits can be provided from CBD in alleviating mental health disorders. Studies have suggested CBD's role as an allosteric modulator of serotonin receptor 5-HT_{1A} [9]. This role in addition to CBD's interaction with anandamide leads to the anxiolytic effects produced by CBD [9]. Even though CBD expresses a low affinity to CB1 receptors, its role in increasing anandamide levels compensates for this leading to activation of CB1 receptors effectively managing the symptoms of anxiety disorders [9]. It is paramount to recognise the critical balance required in anandamide due to its biphasic tendencies [9]. At low doses it acts as an anxiolytic, but it was shown to be ineffective or even anxiety inducing at higher doses [9]. This phenomenon occurs due to the interaction between CBD and TRPV1 at higher doses [9]. Activation of this receptor is mostly anxiety inducing which would worsen symptoms and reverse the initial intention of the treatment [9]. Some studies proposed CBD's benefit as an antidepressant [10]. The results depicted minimised depression and a degree of restoration to the harmful effects caused by cannabis use [10]. The onset of action involved was thought to be through the activation of serotonergic receptors [10]. Despite this, evidence of CBD's antidepressant activity in humans remain limited which sprouts the

importance for further clinical trials to study this effect more closely and establish a more conclusive finding.

By factoring in everything that has been mentioned, we can establish certain uses and risks of cannabis. The lack of regulation remains a big challenge in controlling the potency and safety of cannabis which leads to undesirable effects consequently. Furthermore, the need for further research becomes apparent to solidify the benefits that CBD can bring to several mental illnesses. Moving forward, establishing an optimum dosage and administration of CBD becomes essential to achieve its maximum efficacy. With stricter regulations and increased knowledge of cannabinoids we can achieve a fine balance between the prevention of psychotic related conditions and effective therapeutic activity.

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