Back to the good old marijuana

Rian de Jonge
S3187780
06-04-2021
Faculty of Science & Engineering – University of Groningen
Supervisor: prof. dr. A.J.W. Scheurink

Summary

Over the last five decades, selective breeding of cannabis plants has resulted in an increased potency of the cannabis products available in many countries, including the Netherlands. Overall, concentrations of tetrahydrocannabinol (THC), the main psychoactive component in cannabis, have increased, while concentrations of cannabidiol (CBD) have declined. Much to the pride of the Dutch, Nederwiet is known to have the highest concentrations of THC across Europe. The changing nature of recreational cannabis products has transformed them into a hard drug and can be considered a dangerous trend. Cannabis use leads to an increased risk of developing schizophrenic symptoms due to the actions of THC on the endocannabinoid and dopaminergic system. This risk is increased with frequent use and use of high potency cannabis. Moreover, individuals with a genetic predilection to develop schizophrenia are more prone to crave for the highest potency of cannabis and are more likely to become heavy users. So, the trend of increasing THC concentrations in cannabis is a risk factor for all people and especially worrisome for individuals with a predisposition for schizophrenia and psychotic disorders. On the contrary, CBD can counteract the detrimental effects of THC and the use of cannabis containing both THC and CBD can be protective against THC-induced psychotic symptoms. Due to the constant hunt for increasing potency cannabis, favoring THC over CBD, the natural antipsychotic properties of CBD have been eliminated from cannabis products. As a result, the risk of subsequent psychosis and schizophreniform disorder significantly increased. This has considerable public health implications and shows the importance of raising public awareness of the risks associated with use of high-potency cannabis. Instead of portraying the high potency Nederwiet as “the best marijuana there is”, we should get back to the good old marijuana.

Table of contents

Glossary

Cannabis

- Cannabinoids: Any of a group of closely related compounds found in cannabis.
- Tetrahydrocannabinol (THC): The main psychoactive cannabinoid in cannabis, responsible for most of the intoxicating effects of cannabis.
- Cannabidiol (CBD): A major nonpsychotropic cannabinoid in cannabis.
- Marijuana: A common recreational drug derived from the dried leaves, flowers, seeds or stems of the cannabis plant which is smoked, vaped or ingested to create an intoxicating effect. Also called weed, herb or pot.
- Hash: a concentrated drug derived from the dried resin of the flowers of the cannabis plant. Also called hashish.
- Skunk: High-potency cannabis products derived from selectively bred and genetically modified cannabis plants.

Endocannabinoid system

- Retrograde messengers: Neurotransmitters that are released from postsynaptic neurons and act on presynaptic neurons.
- Depolarization-induced suppression of inhibition: Transient suppression of inhibitory input via a retrograde form of synaptic inhibition following the activity dependent release of endocannabinoids from the postsynaptic cell.
- Agonist: A compound that can bind to and activate a receptor, thus mimicking an endogenous ligand or neurotransmitter.
- Antagonist: A compound that can bind to and block a receptor and thereby block the biological response.

Neurotransmitters

- Dopamine: Neurotransmitter critically involved in mediating reinforcing and rewarding properties of drugs of abuse. Dopamine is also involved in the pathology of schizophrenia and psychotic disorders.
- Glutamate: The main excitatory neurotransmitter in the nervous system.
- Gamma-aminobutyric acid (GABA): The main inhibitory neurotransmitter in the nervous system.

Dopaminergic reward system

- Ventral tegmental area (VTA): A structure in the midbrain which sends dopaminergic projections to both the limbic and cortical areas.
- Nucleus accumbens (NAc): A region in the basal forebrain involved in the reinforcing and addictive behaviors in response to drug use.
- Prefrontal cortex (PFC): A frontal brain region that modulates higher order executive processes, including impulse control and initiation of goal-directed behaviour.
- Ventral pallidum (VP): A structure within the basal ganglia projecting to the VTA.
- Pedunculopontine nuclei (Ppt): A collection of neurons located in the brainstem projecting to the VTA.
- Hippocampus: A region of the brain that is involved primarily in learning and memory.

Chapter 1. Introduction

Cannabis is worldwide the most commonly cultivated, trafficked and abused drug (World Health Organization, 2021). Although production and consumption of cannabis has been illegal in most countries since the 1930s, recreational use of cannabis continued to increase (Room, 2010). Currently, cannabis consumption has an annual prevalence rate of approximately 147 million individuals, indicating that nearly 2.5% of the global population consumes cannabis (World Health Organization, 2021). Over the years, cannabis use has gained increasing acceptance. The general notion seems to be that cannabis is a harmless leisure activity, access to which should not be regulated or considered illegal (Volkow et al., 2014). This has caused tensions and sparked debates about legalizing cannabis.

The Dutch cannabis policy is known to be explicitly tolerant compared to other European nations (MacCoun & Reuter, 1997). In the Netherlands, rules and regulations concerning cannabis are described in the Opium Act. In the Opium Act a distinction is made between hard drugs, placed on Schedule I, and soft drugs, placed on Schedule II (Wettenbank, 2021). Schedule I includes drugs associated with an unacceptable health risk. Cannabis products are placed on Schedule II and are seen as soft drugs with less health risks associated to them. In strict terms, possession, sale and cultivation of cannabis are defined as criminal acts in the Opium Act (Wettenbank, 2021). However, possession and use of cannabis in small quantities has been decriminalized in the Netherlands. Moreover, when following strict regulations set out in the coffee shop policy, coffeeshops are tolerated to sell cannabis products for recreational use (Rijksoverheid, 2021). This depenalization of cannabis has led to a growth in the drug-using population in the Netherlands, with a percentage of cannabis users above the European average (MacCoun & Reuter, 1997).

In addition to this trend of increased cannabis use, a change in the nature of cannabis can be observed (Murray et al., 2016). Over the last five decades, selective breeding of cannabis plants resulted in an increased potency of the cannabis products available in many countries. As a result, concentrations of tetrahydrocannabinol (THC), the main psychoactive component of cannabis, have steadily increased (Murray & Di Forti, 2016). Moreover, novel techniques have resulted in the development of synthetic cannabinoids with even higher potency (Murray & Di Forti, 2016). These forms of high-potency cannabis and synthetic cannabinoids are taking over the market and are viewed as the new designer drugs (Seely et al., 2012).

The ever-increasing potency of cannabis can be considered a dangerous trend. There are publications that show that these forms of high-potency cannabis are especially dangerous for vulnerable groups, including people with a predisposition for schizophrenia or psychosis (Di Forti et al., 2015). This debate has also reached the political arena. In 2011, committee Garretsen advised the Dutch government to consider high-potency cannabis a hard drug by placing it on Schedule I of the Opium Act (Garretsen et al., 2011). In the following chapters, I will put forward arguments supporting this viewpoint by stating that we should ban the use of high-potency cannabis and go back to the good old marijuana.

Chapter 2. Cannabis

Cannabis is a psychoactive drug derived from the plant *Cannabis sativa* (Pierce & Kumaresan, 2006). Although only recently introduced into the Western world, humans have been utilizing cannabis products in various forms throughout recorded history. Reports dating back to the beginning of the Christian era report the use of cannabis as a medicine to relief cramps and rheumatic pain in ancient China (Zuardi, 2006). The first reference of the use of cannabis as a psychoactive drug stems from the Indians, who used cannabis products as hypnotics and tranquilizers. Cannabis was introduced into

Western medicine in the 19th century as a therapeutic alternative for infectious diseases such as cholera and tetanus (Zuardi, 2006). Although the potential of medicinal cannabis has received increasing research attention over recent years, cannabis is now mainly used for recreational use as a stimulant drug in the Western world (Sarris et al., 2020).

Cannabis plants produce a unique family of compounds called cannabinoids. To date, more than a hundred different cannabinoids have been identified (Hanuš, 2009). The two most important and abundant cannabinoids are tetrahydrocannabinol (THC) and cannabidiol (CBD) (Müller-Vahl & Emrich, 2008). Cannabinoids are produced in crystal formations around the flowering tops of the cannabis plant (Murray et al., 2016). As a recreational drug, cannabis is available in the form of dried leaves or flowers, known as marijuana, or in a more concentrated form as dried resin, known as hash (American Addiction Centers, 2021). Hash is the more potent form of cannabis and contains the highest levels of THC. However, THC levels in marijuana have also been increasing in recent years due to efforts in crossbreeding of cannabis plants (Freeman et al., 2019). Products from these genetically modified cannabis plants are also referred to as skunk.

Much to the pride of the Dutch, the Dutch marijuana is known to have the highest concentrations of THC across Europe (Freeman et al., 2019). This so called Nederwiet is the most popular type of cannabis in the Netherlands (Niesink et al., 2015). As depicted in Figure 1, the mean concentration of THC in Nederwiet has risen sharply from 8.6% in 2000 to 14.6% in 2020 (Trimbos Instituut, 2020). Concentrations of THC in Nederwiet are significantly higher than concentrations in more traditional types of marijuana, since marijuana imported from abroad contains on average 4.8% THC (Trimbos Instituut, 2020). Moreover, the attempts to obtain higher concentrations of THC resulted in a decreased concentration of CBD in Nederwiet and a low CBD:THC ratio. Nederwiet currently only contains traces of CBD, with an average CBD concentration of 0.3% (Trimbos Instituut, 2020). Traditional marijuana contains higher concentrations of CBD and still has a higher CBD:THC ratio.

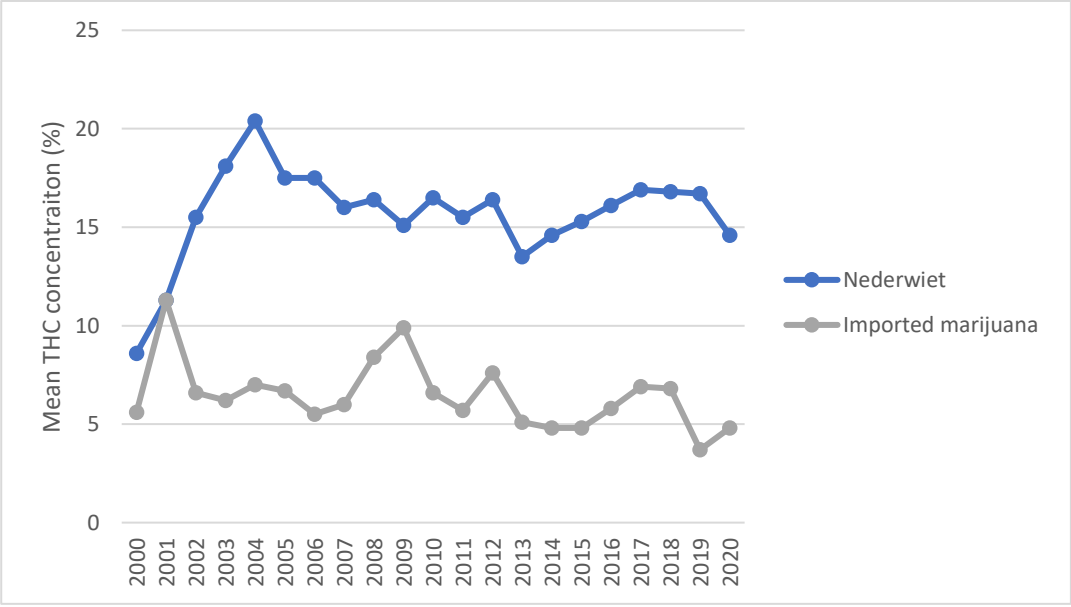

***Figure 1*: Mean concentration of tetrahydrocannabinol (THC) in Nederwiet and imported marijuana from 2000 – 2020.**
Data are presented as means.
Source: Constructed from data obtained from "THC-concentraties in wiet, nederwiet en hasj in Nederlandse coffeeshops 2019/2020" by Trimbos Instituut, 2020, Utrecht: Trimbos-instituut.

Overall, concentrations of THC in cannabis have increased over the years, while concentrations of CBD have declined (Freeman et al., 2019). Novel methods of extracting THC from cannabis plants

have resulted in cannabis products with a THC concentration up to 40% (Murray & Di Forti, 2016) Furthermore, recent technological developments have resulted in the development of synthetic cannabinoids with even higher potency. Over 500 synthetic cannabinoids are available on the internet and have emerged as popular alternatives to marijuana (Seely et al., 2012). But why did this search for increasing potency cannabis occur? What attracts people to start using cannabis, especially the high potency forms?

Chapter 3. The endocannabinoid system

Cannabis exerts its effect primarily by interacting with the endocannabinoid system. The endocannabinoid system comprises the endogenous cannabinoids, cannabinoid receptors and the metabolic pathways responsible for synthesis and degradation (Mackie, 2006).

Endogenous cannabinoids, also called endocannabinoids, are a family of lipophilic ligands that can activate the cannabinoid receptors. To date, five endocannabinoids have been identified, of which anandamide and 2-arachidonoylglycerol are the best studied (Van der Stelt & Di Marzo, 2003). Endocannabinoids are derived from lipid precursors and synthesized on demand during periods of high neuronal activity in a calcium-dependent manner (Di Marzo et al., 1996). Both 2-arachidonoylglycerol and anandamide act as retrograde messengers (Figure 2). Upon stimulation, postsynaptic calcium channels open and the increased intracellular calcium levels will activate enzymes that synthesize endocannabinoids. Endocannabinoids then leave the postsynaptic cell and act presynaptically to inhibit release of excitatory and inhibitory neurotransmitters (Wilson & Nicoll, 2002). Depending on the neuronal circuit, endocannabinoids may thus activate or inhibit neurotransmission (van der Stelt & di Marzo, 2003). After release, endocannabinoids are cleared from the extracellular space by a reuptake mechanism and enzymatic hydrolysis (Murray et al., 2016).

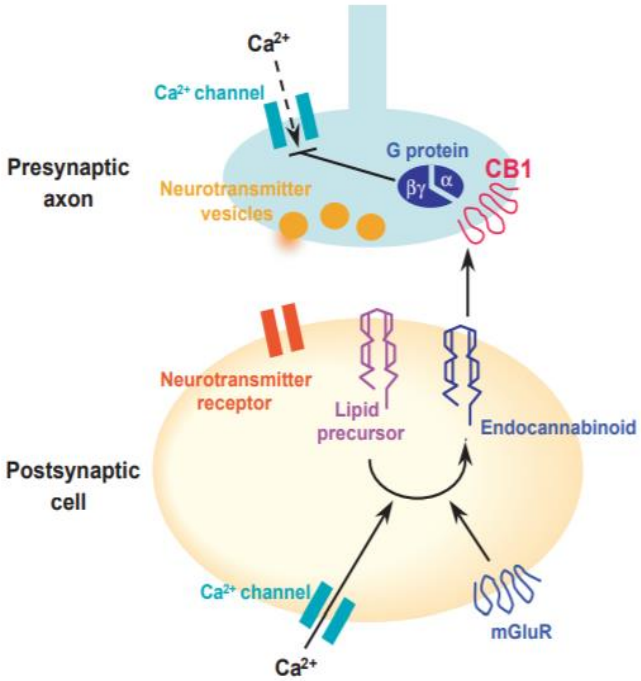

Figure 2: **Retrograde signaling by endocannabinoids**. Postsynaptic depolarization opens voltage-dependent calcium channels. Postsynaptic calcium influx activates enzymes that synthesize endocannabinoids from lipid precursors. Endocannabinoids are released from the postsynaptic cell and activate presynaptic cannabinoid receptors, which directly inhibits presynaptic calcium influx, inhibiting the release of neurotransmitters by the presynaptic cell.
Source: Reprinted from "Endocannabinoid signaling in the brain" (p. 679) by R.A. Wilson & R.I. Nicoll, 2002

Endocannabinoids can bind to and activate two types of G-protein coupled receptors: CB1 and CB2 receptors (Müller-Vahl & Emrich, 2008). CB1 receptors are mainly located on neurons in the central and peripheral nervous system but can also be found throughout the body in organs deputed to reproductive, cardiovascular and gastrointestinal functions (Howlet et al., 2010; Nijenhuis, 2019) (Figure 3). Within the brain, CB1 receptors are mostly concentrated in those areas of the brain that control movement, coordination, sensory perception, learning and memory, reward and emotions, and hormonal function and body temperature (Müller-Vahl & Emrich, 2008; Nijenhuis, 2019). CB2 receptors are mainly located on cells and tissues within the immune system (Müller-Vahl & Emrich, 2008). Recently, mounting evidence is suggesting that some of the actions of

endocannabinoids seem to be mediated by non-CB1/CB2 receptors such as the vanilloid TrpV1 and GPR55 receptors (Gururujan & Malone, 2016).

The wide dispersion of cannabinoid receptors in the human body explains not only the large number of physiological actions of endocannabinoids, but also the effects of cannabis products. In general, endogenous cannabinoids have a basic function to control emotional responses to stress (Piomelli, 2008). They work as stress-recovery factors by protecting the body and making you relax, sleep, forget and eat. In other words: do not worry, be happy! And because THC also binds to and activates the CB1 receptor, cannabis largely exerts the same effects as the endogenous cannabinoids. By binding to the CB1 receptor, THC is responsible for the psychoactive effects of cannabis, which include euphoria, enhanced sensory perception, increased appetite, memory impairment and pain reduction (Van der Stelt & Di Marzo, 2003). And the higher the concentration of THC in cannabis, the stronger this response.

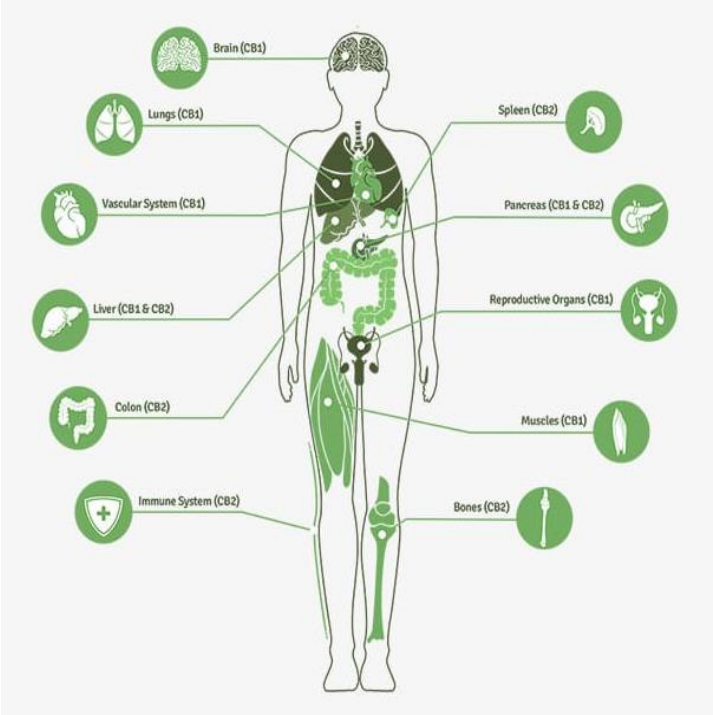

Figure 3: **The location of CB1 & CB2 receptors in the human body.** ***Source:*** Reprinted from "Het ECS" by R. Nijenhuis, 2019 *(https://www.canna-theek.com/blog/het-endocannabinoidesysteem/)*

Despite this variety of physiological effects of cannabis, the primary reason people use cannabis is because of the relaxing, pleasurable feeling it gives (Bianconi et al., 2016). Pleasure is closely associated with the reward system and the neurotransmitter dopamine (Bressan & Crippa, 2005; Spanagel & Weiss, 1999). Much evidence indicates that cannabinoids are key components in the regulation of dopamine neurotransmission in the reward system (Cheer et al., 2007). We will elaborate on this link between cannabinoids and dopamine in the next chapter.

Chapter 4. Cannabinoids in the mesolimbic dopamine system

The dopaminergic reward system is a neural pathway that originates from dopamine neurons in the ventral tegmental area (VTA) of the midbrain (Spanagel & Weiss, 1999). Dopaminergic neurons in the VTA project to, among other areas, the nucleus accumbens (NAc) and the prefrontal cortex (PFC). Therefore, dopaminergic projections are further divided into mesolimbic pathways, projecting to the NAc, and mesocortical pathways, projecting to the PFC (Lupica & Riegel, 2005). Dopamine neuronal firing in the VTA is controlled by excitatory glutamatergic and inhibitory GABAergic inputs, both from GABA interneurons within the VTA and from extrinsic GABAergic neurons from the NAc, the ventral pallidum (VP) and the pedunculopontine nuclei (Ppt) (Lupica & Riegel, 2005) (Figure 4a).

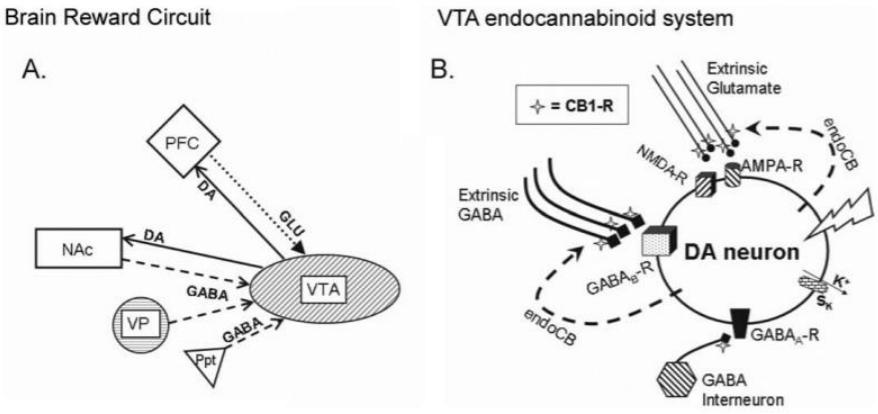

***Figure 4*: The dopaminergic reward system and substrates for endocannabinoid action in the ventral tegmental area (VTA).** (A) A simplified schematic diagram illustrating some of the important inputs and outputs of the VTA. (B) Locations of CB1 receptors and mechanisms of endocannabinoid (endoCB) release in the VTA. The lightning bolt represents the depolarization necessary to initiate endocannabinoid release from VTA dopaminergic neurons. Abbreviations: PPt: pedunculopontine nucleus; VP: ventral pallidum; NAc: nucleus accumbens; PFC: prefrontal cortex; DA: dopamine; GLU: glutamate.
Source: Reprinted from "Endocannabinoid release from midbrain dopamine neurons: A potential substrate for cannabinoid receptor antagonist treatment of addiction" (p. 1106) by C.R. Lupica & A.C. Riegel, 2005

Mesolimbic dopaminergic pathways are known to serve as the final common neural pathway for mediating the positive reinforcing and rewarding properties of all known drugs of abuse, including cannabis (Pierce & Kumaresan, 2006). Endocannabinoid signaling is thought to play a key role in this pathway. Under normal conditions, the GABAergic neurons provide a tonic inhibition of dopaminergic VTA neurons. This inhibition prevents dopamine release in the NAc (Lupica & Riegel, 2005). However, when a stimulus arrives that depolarizes the dopaminergic neuron, endocannabinoids are synthesized in the dopaminergic cell. After release, endocannabinoids travel from the dopaminergic neuron into the extra-synaptic space, where they activate cannabinoid CB1 receptors on presynaptic neurons in a retrograde fashion (Oleson & Cheer, 2012) (Figure 4b). As explained in Figure 2, retrograde activation of CB1 receptors results in inhibition of neurotransmitter release. However, no CB1 receptors are found on the dopaminergic cells in the VTA (Matsuda et al., 1993). This argues against a more direct role for the CB1 receptors in regulating dopamine neuronal activity. In a model proposed by Lupica & Riegel (2005) it is suggested that endocannabinoids might increase dopamine release in the NAc by indirectly disinhibiting dopamine neurons in the VTA.

Within the VTA, CB1 receptors are present on GABA interneurons and GABAergic neurons originating from the NAc (Lupica & Riegel, 2005) (Figure 4b). Via these two pathways, endocannabinoids can modulate activity of dopaminergic cells in the VTA. When endocannabinoids bind to the CB1 receptors located on the GABAergic axons, release of GABA is inhibited. As a result, VTA dopaminergic neurons will receive less inhibitory input through the GABAα and GABAβ receptors, leading to a disinhibition of the dopaminergic neuron. This process is known as depolarization-induced suppression of inhibition (Alger & Kim, 2011). Via this hypothesized mechanism, stimulation of CB1 receptors on GABAergic terminals in the VTA disinhibits dopaminergic neuronal activity, resulting in increased dopamine release in the NAc (Lupica & Riegel, 2005) (Figure 5a). Animal studies supporting this hypothesis showed that the CB1 agonist WIN55,212-2 increased neuronal firing in the VTA and increased dopamine levels in the NAc (Gessa et al., 1998; Tanda et al., 1997). Moreover, this cannabinoid induced increase in dopaminergic neuronal activity was blocked by a GABA receptor antagonist (Cheer et al., 2000). Collectively, these results indicate that endocannabinoids increase the firing rates of dopaminergic VTA neurons by decreasing inhibitory GABAergic tone on these cells (Pierce & Kumaresan, 2006).

However, it should be noted that endocannabinoids can also inhibit glutamatergic transmission in the VTA via a presynaptic mechanism, which could counterbalance the disinhibitory effect (Melis et al., 2004) (Figure 5a). However, within the VTA, depolarization-induced suppression of inhibition should theoretically result in a net disinhibition of dopaminergic neuronal activity, resulting in increased dopamine release (Lupica & Riegel, 2005).

Moreover, retrograde endocannabinoid signaling is necessary for this increase in dopamine. Cheer et al. (2007) showed that when the CB1 receptor antagonist rimonabant was applied, the increase in dopamine release evoked by injection of ethanol was prevented. This indicates that endocannabinoids are required to elevate the constant blockade of GABA on VTA neurons. Since endocannabinoids are released in an activity dependent manner, this ensures that burst firing of dopaminergic neurons only happens in response to stimuli (Wilson & Nicoll, 2002). So, endocannabinoid signaling keeps the mesolimbic reward system in check by making sure that increases in dopamine only happen after sufficient stimulation.

However, exogenous cannabinoids, like THC, can act as direct agonist on CB1 receptors and by that mimic the endogenous cannabinoids (Müller-Vahl & Emrich, 2008). As shown in Figure 5b, THC can bind directly to the CB1 receptors on the GABAergic axons and by that directly inhibit GABA release in a resting state. Whereas the endocannabinoid system only operates on demand after sufficient stimulation, exogenous THC can do so directly and overwhelm the endogenous system (D'souza et al., 2012). Gessa et al. (1998) showed that dopamine cell firing was dose-dependently increased following cumulative dosing with THC, with higher concentrations of THC inducing higher VTA burst firing. This cannabinoid-induced increase in dopamine neural activity was abolished after administration of a CB1 receptor antagonist, which shows that cannabinoids increase dopamine neural activity through a CB1 receptor-dependent mechanism. As shown by Chen et al. (1990), the increased firing of the dopaminergic neuron induced by THC leads to increased dopamine release in the NAc. So, without initial stimulation of the dopaminergic neuron, THC can disinhibit the dopaminergic neuron, leading to an increase in dopamine release in the NAc.

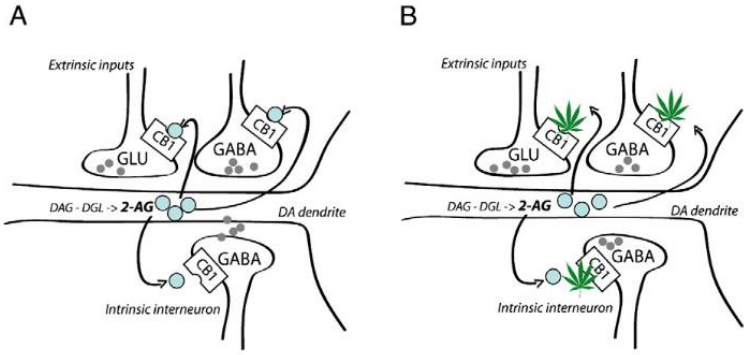

Figure 4: **Cannabinoid signaling in the ventral tegmental area (VTA)**. (A) Firing patterns in VTA dopaminergic (DA) neurons are influenced by excitatory (GLU, indicated in grey) and inhibitory (GABA, indicated in grey) inputs. DA neurons regulate pre-synaptic terminals via retrograde endocannabinoid (2-AG, indicated in blue) signaling at CB1 receptors in an activity-dependent manner. (B) When exogenous cannabinoids (THC, indicated by cannabis leaves) bind to CB1 receptors located on glutamatergic (GLU) and GABAergic (GABA) terminals, retrograde endocannabinoid (2-AG) signaling is disrupted and stimulation of CB1 receptors by THC inhibits glutamate and GABA release, resulting in a net disinhibition of DA neurons. ***Source:*** Reprinted from "Does dopamine mediate the psychosis-inducing effects of cannabis? A review and integration of findings across disciplines" (p.110) by R. Kuepper, P.D. Morrison, J. van Os, R.M. Murray, G. Kenis & C. Henquet, 2010.

The bottom-line is that the action of both endogenous and exogenous cannabinoids in the mesolimbic system can lead to an increase in dopamine release. Endocannabinoids act in an activity-dependent manner as retrograde messengers, while THC can do so directly. Moreover, THC can bind more tightly to the CB1 receptor and dissociate more slowly than endogenous cannabinoids. The newly developed synthetic cannabinoids can bind to the CB1 receptor with even higher affinity, as they are synthesized as full agonists of the CB1 receptor (Seely et al., 2012). Subsequently, regular

consumption of high potency cannabis leads to a strong, constant disinhibition of dopaminergic neurons in the VTA. As a result, dopamine will be released in high amounts, resulting in a hyperfunctioning of the dopaminergic system. This increase in dopamine levels in the NAc is theorized to mediate the primary positive reinforcing and rewarding properties of cannabis (Wise & Bozarth, 1985). This is what makes consumption of cannabis with high concentrations of THC rewarding and pleasurable. However, increasing dopamine levels are also related to schizophrenia and psychotic disorders (Kuepper et al., 2010).

Chapter 5. Cannabis consumption & schizophrenia

Schizophrenia is a psychiatric disorder characterized by impairments in the perception of reality (Müller-Vahl & Emrich, 2008). The disorder is known to be a major cause of disability associated with decreased quality of life and life expectancy. Internationally, the life-time prevalence of schizophrenia is approximately 0.5-1.0% (Müller-Vahl & Emrich, 2008). According to the latest population screening in 2010, an estimated 0.5% of the Dutch population aged 18 to 65 years old has or has had schizophrenia at some point in their life (De Graaf et al., 2010). As described in the Diagnostic and Statistical Manual of Mental disorders, schizophrenia is characterized by a wide variety of symptoms which must be persists for at least six months for someone to be diagnosed with schizophrenia. Most often, the symptoms are subclassified into positive symptoms, including delusions, hallucinations and disorganized thinking, negative symptoms, including flattened emotion, poverty of speech and social withdrawal, and cognitive deficits, including memory impairments and reduced executive functioning (Tandon et al., 2013). The presence of delusions or hallucinations is also known as psychotic disorder. Psychosis describes the positive symptoms, whereas schizophrenia is a developmental disorder that includes severe psychotic symptoms. Both schizophrenia and psychotic disorder are part of the schizophrenic spectrum (Pearson & Berry, 2019).

To date, schizophrenia is still one of the most mysterious diseases. It is assumed that complex interactions between genetic and environmental factors, neurobiological alternations as well as psychological and social processes contribute to the multifactorial pathogenesis of schizophrenia (Van Os et al., 2008; Müller-Vahl, 2008). Neuroimaging studies have shown a reduction in brain volume in schizophrenic patients, especially in temporal and limbic structures like the hippocampus and amygdala, as well as abnormalities in activation patterns in the PFC (Steen et al., 2006). In addition, schizophrenia and psychotic symptoms have been traditionally linked to the neurotransmitter dopamine (Meltzher & Stahl, 1976; Kuepper et al., 2010). The classic dopaminergic hypothesis of schizophrenia states that the positive symptoms in schizophrenia are caused by an overactivation of the mesolimbic dopaminergic system. Theorized by Kapur et al. (2005), a hyperdopaminergic state in the mesolimbic system disrupts the process of salience attribution, which ultimately leads to delusion and psychotic symptoms. In line with this hypothesis, anti-schizophrenic drugs which block dopamine receptors are effective in treating positive symptoms in schizophrenia (Carlson, 1978). Moreover, elevated presynaptic dopamine function is found in schizophrenic patients (Howes & Kapur, 2009). Later versions of the dopaminergic hypothesis also propose that reduced dopaminergic activity in the prefrontal cortical brain regions might be associated with the negative and cognitive symptoms (Lynch, 1992).

As explained in chapter 4, administration of exogenous cannabinoids can lead to enhanced mesolimbic dopamine release via their action on CB1 receptors. Since schizophrenia and psychosis can result from an overactive dopaminergic system, this highlights cannabis consumption as a potential risk factor for schizophrenia. Indeed, evidence from prospective epidemiology studies support a causal link between cannabis and psychotic symptoms.

The first indication of a causal link between cannabis use and schizophrenia came from a longitudinal study in a cohort of 45,570 Swedish conscripts (Andreasson et al., 1987). In this study, data regarding drug use was obtained via a questionnaire at baseline and in-patient admissions for psychiatric care were followed during a 15-year follow-up period. Results showed that individuals who reported using cannabis at least once were 2.4 times more likely to be admitted for schizophrenia over the subsequent 15-year period compared to non-users. Moreover, the risk of later schizophrenia increased with increasing cannabis consumption. Heavy users, who reported using cannabis more than 50 times, were 6.0 times more likely to have developed later schizophrenia than non-users (Andreasson et al., 1987). However, more than half of these heavy users had a psychiatric diagnosis other than psychosis at conscription, and when this confound was controlled for the relative risk decreased to 2.3. Nonetheless, the authors concluded that these findings indicate that cannabis is an independent risk factor for schizophrenia and "should thus be viewed as an additional clue to the still elusive etiology of schizophrenia" (Andreasson et al., 1987, p. 1485).

There has now been a wealth of studies investigating the link between cannabis use and schizophrenia and psychotic symptoms. Later studies, considering confounding, bias, misclassification, reverse causation, and other explanations for the association, also concluded that cannabis use significantly increases the risk of psychotic disorders (Gage et al., 2016). Overall, cannabis use confers a twofold increase in the relative risk for later schizophrenia (Arsenault et al. 2004). This risk seems to be increased with higher levels of cannabis use, with an almost 4 times increased risk of psychotic symptoms among the heaviest users (Marconi et al., 2016). However, since not all adults with schizophrenia have used cannabis, cannabis use is not a necessary cause for the development of schizophrenic symptoms. Moreover, cannabis use is also not a sufficient cause for development of symptoms, since the majority of cannabis users do not develop schizophrenia (Andreasson et al., 1987). Therefore, a causal link between cannabis use and schizophrenia cannot be unequivocally established (Marconi et al., 2016). However, there is a strong association, making cannabis a component cause, forming part of a causal constellation that leads to schizophrenia (Arsenault et al., 2004).

The increased risk of schizophrenic symptoms after cannabis consumption can be attributed to the actions of THC on the dopaminergic system. This raises concerns as to whether the recent trend of increasing concentrations of THC in cannabis poses a greater risk for the development of schizophrenia. Di Forti et al. (2015) sought to test the hypothesis if daily use of high-potency cannabis is associated with a particularly high risk of psychosis. In a case-control study in South London, Di Forti et al. (2015) examined cannabis consumption patterns in 461 patients with a first episode of psychotic disorder and 389 healthy controls. They obtained data about history of cannabis use, frequency of cannabis consumption and type of cannabis used, discriminating between low potency hash, on average 2-4% THC, and high potency skunk, on average 12-18% THC. Via logistic regression, Di Forti et al. (2015) showed that individuals who used low-potency hash had no increased risk of psychotic disorder compared to non-users. However, as shown in Figure 6, individuals who used high potency skunk-like cannabis were almost twice as likely to be diagnosed with a psychotic disorder if they used it less than once per week, nearly three times as likely if they used it at weekends, and more than five times as likely if they were daily users. These results support the hypothesis that use of high-potency cannabis confers an increased risk of psychotic symptoms compared to traditional low-potency cannabis. Moreover, the strongest predictor for later psychosis was daily use of high potency cannabis (Di Forti et al., 2015).

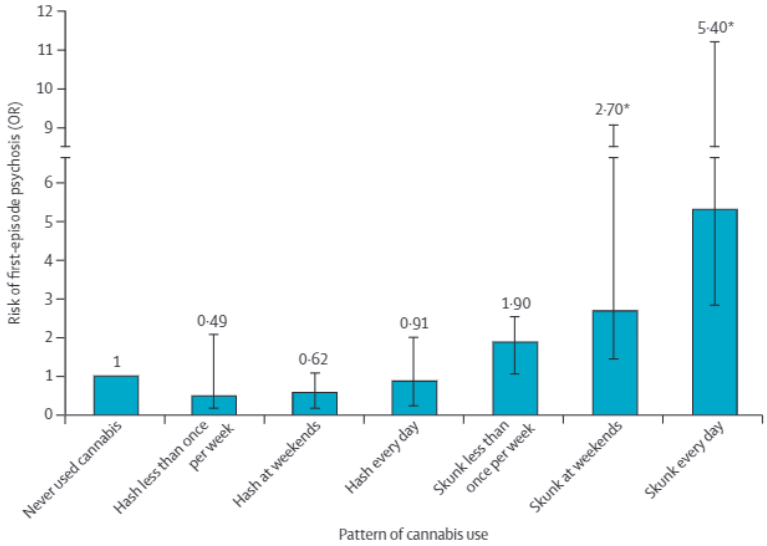

Figure 6: **Probability of individuals having a psychotic disorder by pattern of cannabis use**. Abbreviations: OR: odds ratio. *p<0.05

Source: Reprinted from "Proportion of patients in south London with first-episode psychosis attributable to use of high potency cannabis: a case-control study" (p.237) by M. Di Forti, A. Marconi, E. Carra, S. Fraietta, A. Trotta, M. Bonomo, … & R. M. Murray, 2015.

One limitation to this study is that it was based on retrospective self-reports of cannabis consumption. To establish temporal priority, data on cannabis consumption should be obtained before onset of symptoms. Therefore, causality could not be determined. However, a follow-up study across Europe replicated the same strong effect of daily use of high-potency cannabis on the odds ratio for psychotic disorder. Additionally, it was shown that, assuming causality, removing high-potency cannabis use could prevent up to 50% of new cases of psychotic disorder in Amsterdam (Di Forti et al., 2019). Moreover, recent evidence also suggest that chronic psychotic disorders can occur as a result of persistent usage of synthetic cannabinoids (Fattore, 201 6; Hurst et al., 2011). Taken together, Di Forti et al. (2015) concluded that these findings "show the importance of raising public awareness of the risks associated with use of high-potency cannabis" (Di Forti et al., 2015, p. 237).

The effect of THC on the mesolimbic dopamine system is only one mechanism that could explain the increased risk of schizophrenic symptoms associated with cannabis use. Concentrations of CB1 receptors are also high in the hippocampus and PFC, regions also heavily involved in the symptomatology of schizophrenia (Freund et al., 2003). Mounting evidence shows that THC can also influence these brain regions, which may explain the negative and cognitive symptoms seen in schizophrenia and can also contribute to psychotic symptoms (Auclair et al., 2000; D'Souza et al., 2004; Hoffman & Lupica, 2000). However, these mechanisms remain to be tested further.

In addition, studies have showed that cannabis use increases the risk for psychotic symptoms especially in individuals with an established vulnerability for psychosis. Henquet et al. (2005) showed that the psychomimetic effect of THC was much stronger in individuals predisposed to the development of psychotic illness. Van Os et al. (2002) also reported that individuals with established vulnerability to schizophrenia had a much worse outcome when using cannabis. Several candidate genes have been hypothesized to modify the risk of developing schizophrenia after cannabis exposure. Carriers of these genetic variants were much more likely to develop schizophreniform disorder if they used cannabis (Caspi et al., 2015; Morgan et al., 2016). In line with the second-hit model of schizophrenia proposed by Zubin & Spring (1977), individuals might be genetically susceptible to schizophrenia but not get the disease unless it is triggered by some life-event stressors. Cannabis use can be such a stressor, which has a relatively weak individual effect, but in a

genetically susceptible individual it may provide the second hit which leads to the development of schizophrenia (Davis et al., 2016).

Cannabis use can thus be seen as an independent risk factor for the emergence of schizophrenic symptoms. This risk is increased with higher concentrations of cannabis and daily use and individuals with a vulnerability to psychotic disorders are especially sensitive to its effects. This already highlights high potency cannabis use as a risk factor, especially for vulnerable people. But there is more, since the relationship between cannabis use and schizophrenia works in two ways.

Chapter 6. Schizophrenia & cannabis consumption

Substance abuse is extremely prevalent in schizophrenic patients. Rates of cannabis use are approximately two times as high among schizophrenics compared to individuals without mental illness (Van Os et al., 2002). Moreover, it is known that patients with psychotic symptoms are more likely to be heavy users and are more prone to crave for high-potency cannabis. Di Forti et al. (2009) found that patients with first episode psychosis were 6.4 times more likely to be current daily users. Among those who used cannabis, 78% of the psychotic patients used high-potency cannabis compared to 37% of the control group (Di Forti et al., 2009). This high prevalence of cannabis use in schizophrenics is most commonly explained by the self-medication hypothesis. The self-medication hypothesis states that patients use drugs to alleviate disease symptoms or medication side-effects (Khantzian, 1997). In this view, substance use is a mere symptom of the schizophrenic disease and would disappear with the relief of symptoms. But in reality, drug use generally leads to an exacerbation of symptoms in schizophrenic patients, and yet their drug use persists (Potvin et al., 2003). An additional hypothesis proposed by Chambers et al. (2001) suggests that schizophrenic patients may have a predilection for addictive behavior as a primary disease symptom. This primary addiction hypothesis suggests that the increased vulnerability for drug addiction results from neurodevelopmental alternations in individuals with a susceptibility for schizophrenia.

As explained before, schizophrenic symptoms are associated with an overactivity of the mesolimbic dopaminergic system. This increased dopamine release in the NAc not only leads to schizophrenic symptoms but is also involved in mediating drug craving and the reinforcing effects of drugs of abuse, including cannabis (Kuepper et al., 2010; Wise & Bozarth, 1985). Increased dopamine levels in the NAc are associated with increased reward and craving and therefore links to addictive behaviour. It is hypothesized that the increased vulnerability to addiction may reflect the impact of the neuropathology of schizophrenia on the neural circuitry mediating drug reward and reinforcement (Chambers et al., 2001).

Neurons in NAc receive input from the PFC, hippocampus and VTA and integration of these signals contributes to the motivational consequences of drugs of abuse (Chambers et al., 2001) (Figure 7a). Normally, afferents from the hippocampal formation provide excitatory input to the PFC and NAc. Glutamatergic afferents from the PFC provide inhibitory control over the NAc. In the NAc, the input from the PFC and hippocampus is integrated with dopaminergic afferents from the VTA to regulate motivational processes and reward. Withing this circuit, the PFC acts as a strong impulse inhibitor, inhibiting the NAc and drug seeking behaviour. A dysfunctional integration of the inputs to the NAC in schizophrenics could alter propensity for addictive behaviour (Chambers et al., 2001). Although the primary neuropathology in schizophrenia remains unclear, schizophrenic patients are known to have reduced volume of the hippocampus (Arnold et al., 1995). As a result, the hippocampus provides less excitatory input to the PFC, leading to reduced PFC functioning. This disrupts the inhibition of the PFC to the NAc, resulting in a failure of executive control over NAc neurons. As a result of this reduction in cortical input, the NAc becomes hyperresponsive to the dopaminergic input from the VTA (Figure 7b). This makes schizophrenic patients more sensitive to the reinforcing effects of drugs, resulting in

a strong craving and motivation to take drugs (Chambers et al., 2001). When the PFC is no longer in control, dopamine-mediated behaviour is no longer inhibited, making it harder to resist the drugs. Thus, a patient with schizophrenia has a genetic background making them especially vulnerable for the reinforcing effects of drugs of abuse.

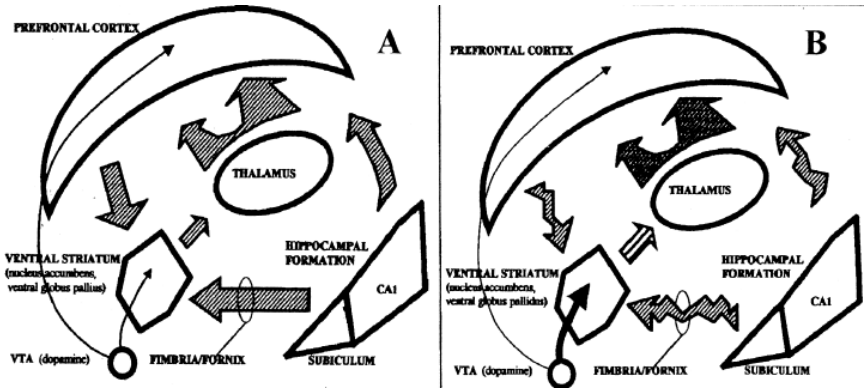

Figure 7: **The neural network implicated in reward, drug addiction and schizophrenia.** (A) Excitatory afferents to the nucleus accumbens (NAc) and prefrontal cortex (PFC) from the hippocampal formation relay contextual information relevant to reward and motivation. Excitatory afferents from the PFC relay inhibitory information to the NAc relevant to regulation of thought and motivation. In the NAc, glutamatergic afferents from the hippocampus and the PFC interact with dopaminergic afferents from the ventral tegmental area (VTA) to regulate motivational processes. (B) In both schizophrenia and drug addiction, a functional disorganization of afferent excitatory communication to the NAc contributes to relative hyperresponsivity to dopaminergic input from the VTA, increasing motivational salience of drugs and drug-related stimuli. In schizophrenia, dysregulation of hippocampal outputs due to developmental abnormalities disrupts PFC communication to the NAc, weakening inhibitory influence on motivational processes. Dopamine: black arrow. Glutamate: striped arrow. ***Source***: Reprinted from "A neurobiological basis for substance abuse comorbidity in schizophrenia" (p.75) by R.A. Chambers, J.H. Krystal & D.W. Self, 2001.

This altered integration of cortical inputs is also seen in the brain of long-term addicts. Long-term substance abuse disrupts functioning of the PFC, which reduces inhibitory control over drug intake (Goldstein & Volkow, 2011). In this view, the brain of a schizophrenic patient is similar to the brain of a long-term addict (Figure 7b). Abnormalities in the hippocampal formation facilitate the positive reinforcing effects of drug reward and reduce inhibitory control over drug-seeking behaviour. This dysregulated integration of dopamine and glutamate signaling in NAc produces changes similar to long-term substance abuse, but without the necessity of prior drug exposure (Chambers et al., 2001).

Thus, because of alternations in the brain, individuals with a susceptibility for schizophrenia have a genetic background that are risk factors to develop addiction. A hyperresponsivity to the reinforcing effects of drugs and a reduction of inhibitory control leads to higher drug craving, resulting in a dysfunctional brain reward system. This makes them more vulnerable for addiction and more likely to become heavy drug users.

Moreover, schizophrenic patients are especially prone to crave for cannabis because of changes in the endocannabinoid system. Zavitsanou et al. (2004) showed a 64% increase in specific binding of CB1 receptors in schizophrenic patients compared with healthy controls. Newell et al. (2006) also showed an increased density of CB1 receptors in the brains of schizophrenic patients. These results indicate that schizophrenic patients have a greater sensitivity in endogenous cannabinoids systems. Since cannabis, especially THC, acts at the endocannabinoid system, schizophrenics are more sensitive to the effects of THC. Taken together, these findings explain why individuals with a genetic predisposition for schizophrenia are more likely to become heavy cannabis users and crave for high potency cannabis.

And this is problematic. Cannabis use after schizophrenia spectrum diagnosis leads to more and earlier relapses with worsening of symptoms and extended hospitalization even in patients stable on

antipsychotics (Hahn, 2018). Moreover, daily users of high-potency cannabis experience their first episode of psychosis, on average, 6 years younger than never-users (Di Forti et al., 2014). Heavy cannabis use generally exacerbates psychotic symptoms, leading to a poor prognosis (Bagot et al., 2015).

Concluding, the relationship between cannabis and schizophrenia works in two ways. Cannabis use, especially daily use of high potency cannabis, leads to an increased risk of developing schizophrenic symptoms. In addition, individuals with a vulnerability for schizophrenia are more prone to crave for high-potency cannabis and they require higher doses. It is not only the drug that may cause schizophrenia, but people that have genetic background to develop schizophrenia are risk factors by itself. So, higher concentrations of THC in cannabis are risk factors, especially for people with genetic vulnerability for psychosis and schizophrenia.

But on the other hand, there are also reports showing a therapeutic effect of cannabis (Colizzi et al., 2020). These effects may be attributed to the other component of cannabis, the cannabinoid CBD.

Chapter 7. Cannabidiol

Cannabidiol, CBD, is a prominent nonpsychotropic constituent of cannabis. Contrary to THC, CBD does not activate CB1 and CB2 receptors and has at most subtle subjective effects and no psychoactive properties (Manini et al., 2015). Due to this apparent lack of effect of CBD, research has focused primarily on the psychoactive properties of THC. However, recently there has been a growing interest in CBD, highlighting its actions and potential therapeutic effect (Burstein, 2015). Emerging evidence suggests that CBD has anticonvulsive, anti-inflammatory, anti-anxiety, antinausea and antirheumatioid properties (Müller-Vahl & Emrich, 2008; Burstein, 2015). Ongoing research highlights the potential of cannabidiol in the treatment of epilepsy, inflammatory and neurodegenerative diseases and cancer (Morales & Reggio, 2019; Gaston & Szaflarski, 2018; Seltzer et al., 2020). Moreover, CBD has shown to have an antipsychotic effect, an effect opposite compared to the psychotogenic effects of THC (Hahn, 2018). This proposes a role for cannabidiol in the treatment of schizophrenia (Gururajan & Malone, 2016).

The first reports of the antipsychotic properties of CBD date back to the previous century. Zuardi et al. (1995) showed that a 4-week treatment with CBD significantly improved symptoms in a 19-year-old female with treatment-resistant schizophrenia. These results were corroborated by Leweke et al. (2012) in a clinical trial in 42 patients suffering from acute schizophrenia and schizophreniform psychosis. Leweke et al. (2012) found that treatment with CBD markedly reduced acute psychotic symptoms. In addition, the antipsychotic effect of CBD was comparable to the effect of the antipsychotic drug amisulpride, but with fewer side-effects.

The clinical benefits of CBD treatment may result from several possible mechanisms. Although much remains unknown, it is hypothesized that CBD has a broad spectrum of pharmacological actions (Hahn, 2018). It has been suggested that CBD acts as a partial antagonist at CB1 receptors, targets the GPR55 and vanilloid TrpV1 receptors and inhibits the uptake and hydrolysis of endocannabinoids (Gururajan & Malone, 2016). However, no target can be denoted as ‘the’ target mechanism of CBD at this point.

Traditionally, cannabis products contain both CBD and THC. As described in the previous chapters, THC is the main psychoactive component of cannabis, responsible for its relaxing effects but also the psychosis-inducing effects through its actions on the endocannabinoid and dopaminergic system. In contrast, CBD is known to have antipsychotic properties. This leads to the hypothesis that CBD might

act as an antipsychotic agent that is able to counteract some of the THC-induced psychotropic effects.

Morgan & Curran (2008) used hair analytic techniques to examine levels of THC and CBD in hair samples of 140 individuals. Participants were divided into three groups: individuals with THC only in their hair (THC only), individuals with both THC and CBD in their hair (THC + CBD) and individuals without cannabinoids in their hair. Severity of psychotic symptoms was assessed via a questionnaire. Results of the study showed that the THC only group showed higher levels of positive schizophrenia-like symptoms compared with the THC + CBD group and the no cannabinoid group. These findings reveal that smoking strains of cannabis containing both THC and CBD can be protective against the psychotic-like symptoms induced by THC alone (Morgan & Curran, 2008). But, as explained in chapter 6, it is known that individuals with a proneness to develop schizophrenia are more likely to be frequent users of high-potency cannabis. Differences in genetic vulnerability to schizophrenia between the three groups could have drawn them to smoke different strains of cannabis, which would provide an alternative explanation to the findings of the study by Morgan & Curran (2008). However, this is unlikely, since no significant differences in the mean level of THC were found between the THC only group and the THC + CBD group and patterns of other drug use were also similar. Moreover, results were corroborated by Schubart et al. (2011) who revealed that smokers of cannabis strains with a high CBD content showed lower psychotic symptoms than smokers of low-CBD cannabis. In addition, pretreatment with CBD in healthy volunteers prevents the psychotic symptoms induced by THC (Bhattacharyya et al., 2010). Together these findings suggest that CBD can counteract the detrimental effects of THC and that the use of cannabis containing both THC and CBD may be protective against THC-induced psychotic symptoms.

Moreover, there are indications that CBD can dampen the reinforcing effects of THC (Morgan et al., 2010). Through this mechanism, CBD may not just reduce the deleterious effects of THC but also reduce cannabis consumption itself. Since heavy cannabis abuse is highly prevalent in schizophrenic patients and results in a poor prognosis, CBD treatment may be especially valuable for schizophrenic patients with comorbid substance abuse (Hahn, 2018).

Genetical manipulation and crossbreeding of cannabis plants have resulted in cannabis products with increasing concentrations of THC. As an unwanted side effect, concentrations of CBD have steadily decreased, resulting in a distorted CBD:THC ratio. Currently, Nederwiet has a CBD concentration of 0.3%, a concentration too low to have any positive effect (Trimbos Instituut, 2020). More traditional forms of marijuana still contain higher concentrations of CBD. Cannabis consumers are often unaware of the CBD:THC ratio because CBD has no noticeable psychoactive effect in humans (Murray & Di Forti, 2016). However, CBD concentrations in cannabis are highly relevant, as it exerts a neuroprotective effect counteracting the psychotropic effects of THC (Hahn, 2018). Due to the constant hunt for increasing potency cannabis, favoring THC over CBD, we have eliminated the natural antipsychotic properties of CBD, essentially turning cannabis into a hard drug. As a result, the risk of subsequent psychosis and schizophreniform disorder significantly increased. The incidence of schizophrenia is much higher in countries like England and The Netherlands where high-potency marijuana has taken over the market compared with countries such as Italy where more traditional forms of marijuana are smoked (Murray & Di Forti, 2016). So, instead of portraying the high potency Nederwiet as “the best marijuana there is”, we should get back to the good old marijuana.

Chapter 8. Conclusion

Worldwide, cannabis use is increasing, as is the concentration of THC in cannabis products. At the same time, the concentration of CBD is decreasing. While cannabis use is still generally considered a harmless leisure activity, the changing nature of cannabis products has transformed them into a hard

drug. Cannabis users are at increased risk of developing schizophrenic symptoms because of the actions of THC on the endocannabinoid and dopaminergic system. This risk is increased with frequent use of high potency cannabis. To make matters worse, individuals with a genetic predilection to develop schizophrenia are more likely to crave for the highest potency of cannabis and are more likely to become heavy users. So, the trend of increasing THC concentrations in cannabis is a risk factor for all people and especially worrisome for individuals with a predisposition for schizophrenia and psychotic disorders. We should shift the focus away from the heated debate about legalizing cannabis use or not and start spreading the public health message outlining the risks associated with the consumption of cannabis, especially of high potency cannabis and synthetic cannabinoids. Moreover, we should not only ban the high concentrations of THC, but also go back to the good old marijuana, with higher concentrations of the antipsychotic cannabinoid CBD. In my view, the arguments put forward in this report provide sufficient evidence to justify such harm-prevention programmes.

References

Alger, B. E., & Kim, J. (2011). Supply and demand for endocannabinoids. *Trends in neurosciences*, 34(6), 304-315.

American Addiction Centers (2021). Quit abusing marijuana. Retrieved on March 23, 2021 from https://sunrisehouse.com/quit-abusing-marijuana/hashish/

Andréasson, S., Engström, A., Allebeck, P., & Rydberg, U. (1987). Cannabis and schizophrenia a longitudinal study of Swedish conscripts. *The Lancet*, 330(8574), 1483-1486.

Arnold, S. E., Franz, B. R., Gur, R. C., Gur, R. E., Shapiro, R. M., Moberg, P. J., & Trojanowski, J. Q. (1995). Smaller neuron size in schizophrenia in hippocampal subfields that mediate cortical-hippocampal interactions. *The American journal of psychiatry,* 152(5), 738–748.

Arseneault, L., Cannon, M., Witton, J., & Murray, R. M. (2004). Causal association between cannabis and psychosis: examination of the evidence. *The British journal of psychiatry*, 184(2), 110-117.

Auclair, N., Otani, S., Soubrie, P., & Crepel, F. (2000). Cannabinoids modulate synaptic strength and plasticity at glutamatergic synapses of rat prefrontal cortex pyramidal neurons. *Journal of neurophysiology*, 83(6), 3287-3293.

Bagot, K. S., Milin, R., & Kaminer, Y. (2015). Adolescent initiation of cannabis use and early-onset psychosis. *Substance abuse*, 36(4), 524-533.

Bhattacharyya, S., Morrison, P. D., Fusar-Poli, P., Martin-Santos, R., Borgwardt, S., Winton-Brown, T., ... & McGuire, P. K. (2010). Opposite effects of Δ-9-tetrahydrocannabinol and cannabidiol on human brain function and psychopathology. *Neuropsychopharmacology*, 35(3), 764-774.

Bianconi, F., Bonomo, M., Marconi, A., Kolliakou, A., Stilo, S. A., Iyegbe, C., ... & Di Forti, M. (2016). Differences in cannabis-related experiences between patients with a first episode of psychosis and controls. *Psychological Medicine*, 46(5), 995-1003.

Bressan, R. A., & Crippa, J. A. (2005). The role of dopamine in reward and pleasure behaviour–review of data from preclinical research. *Acta Psychiatrica Scandinavica*, 111, 14-21.

Burstein, S. (2015). Cannabidiol (CBD) and its analogs: a review of their effects on inflammation. *Bioorganic & medicinal chemistry*, 23(7), 1377-1385.

Carlsson, A. (1978). Antipsychotic drugs, neurotransmitters, and schizophrenia. *American Journal of Psychiatry*, 135(2), 164-173.

Caspi, A., Moffitt, T. E., Cannon, M., McClay, J., Murray, R., Harrington, H., ... & Craig, I. W. (2005). Moderation of the effect of adolescent-onset cannabis use on adult psychosis by a functional polymorphism in the catechol-O-methyltransferase gene: longitudinal evidence of a gene X environment interaction. *Biological psychiatry*, 57(10), 1117-1127.

Chambers, R. A., Krystal, J. H., & Self, D. W. (2001). A neurobiological basis for substance abuse comorbidity in schizophrenia. *Biological psychiatry*, 50(2), 71-83.

Cheer, J. F., Marsden, C. A., Kendall, D. A., & Mason, R. (2000). Lack of response suppression follows repeated ventral tegmental cannabinoid administration: an in vitro electrophysiological study. *Neuroscience*, 99(4), 661-667.

Cheer, J. F., Wassum, K. M., Sombers, L. A., Heien, M. L., Ariansen, J. L., Aragona, B. J., ... & Wightman, R. M. (2007). Phasic dopamine release evoked by abused substances requires cannabinoid receptor activation. *Journal of Neuroscience*, 27(4), 791-795.

Chen, J., Paredes, W., Li, J., Smith, D., Lowinson, J., & Gardner, E. L. (1990). Δ 9-Tetrahydrocannabinol produces naloxone-blockable enhancement of presynaptic basal dopamine efflux in nucleus accumbens of conscious, freely-moving rats as measured by intracerebral microdialysis. *Psychopharmacology*, 102(2), 156-162.

Colizzi, M., Ruggeri, M., & Bhattacharyya, S. (2020). Unraveling the intoxicating and therapeutic effects of cannabis ingredients on psychosis and cognition. *Frontiers in psychology*, *11*.

Davis, J., Eyre, H., Jacka, F. N., Dodd, S., Dean, O., McEwen, S., ... & Berk, M. (2016). A review of vulnerability and risks for schizophrenia: beyond the two-hit hypothesis. *Neuroscience & Biobehavioral Reviews*, 65, 185-194.

De Graaf, R., Ten Have, M., & van Dorsselaer, S. (2010). *De psychische gezondheid van de Nederlandse bevolking. Nemesis-2: Opzet en eerste resultaten.* Utrecht: Trimbos-Instituut.

Di Forti, M., Marconi, A., Carra, E., Fraietta, S., Trotta, A., Bonomo, M., ... & Murray, R. M. (2015). Proportion of patients in south London with first-episode psychosis attributable to use of high potency cannabis: a case-control study. *The Lancet Psychiatry*, 2(3), 233-238.

Di Forti, M., Morgan, C., Dazzan, P., Pariante, C., Mondelli, V., Marques, T. R., ... & Murray, R. M. (2009). High-potency cannabis and the risk of psychosis. *The British Journal of Psychiatry*, 195(6), 488-491.

Di Forti, M., Sallis, H., Allegri, F., Trotta, A., Ferraro, L., Stilo, S. A., ... & Murray, R. M. (2014). Daily use, especially of high-potency cannabis, drives the earlier onset of psychosis in cannabis users. *Schizophrenia bulletin*, 40(6), 1509-1517.

Di Marzo, V., Fontana, A., Cadas, H., Schinelli, S., Cimino, G., Schwartz, J. C., & Piomelli, D. (1994). Formation and inactivation of endogenous cannabinoid anandamide in central neurons. *Nature*, 372(6507), 686-691.

D'souza, D. C., Fridberg, D. J., Skosnik, P. D., Williams, A., Roach, B., Singh, N., ... & Mathalon, D. (2012). Dose-related modulation of event-related potentials to novel and target stimuli by intravenous Δ 9-THC in humans. *Neuropsychopharmacology*, 37(7), 1632-1646.

D'Souza, D. C., Perry, E., MacDougall, L., Ammerman, Y., Cooper, T., Braley, G., ... & Krystal, J. H. (2004). The psychotomimetic effects of intravenous delta-9-tetrahydrocannabinol in healthy individuals: implications for psychosis. *Neuropsychopharmacology*, 29(8), 1558-1572.

Fattore, L. (2016). Synthetic cannabinoids—further evidence supporting the relationship between cannabinoids and psychosis. *Biological psychiatry*, 79(7), 539-548.

Freeman, T. P., Groshkova, T., Cunningham, A., Sedefov, R., Griffiths, P., & Lynskey, M. T. (2019). Increasing potency and price of cannabis in Europe, 2006–16. *Addiction*, 114(6), 1015-1023.

Freund, T. F., Katona, I., & Piomelli, D. (2003). Role of endogenous cannabinoids in synaptic signaling. *Physiological reviews,* 83(3), 1017-1066.

Gage, S. H., Hickman, M., & Zammit, S. (2016). Association between cannabis and psychosis: epidemiologic evidence. *Biological psychiatry*, 79(7), 549-556.

Garretsen, H.F.L., Blom, T., van de Bunt, H., Jespers, J.A.F.J., van Laar, M., Lousberg, R.J.J.C., van de Mheen, D., van Spierenburg, C.J.W.M., de Vries, I., Bonn, M.A.C.L.M., Hollemans, K. (2011). *Drugs in lijsten: rapport Expertcommissie Lijstensystematiek Opiumwet*. Amsterdam: University of Amsterdam.

Gaston, T. E., & Szaflarski, J. P. (2018). Cannabis for the treatment of epilepsy: an update. *Current neurology and neuroscience reports*, 18(11), 1-9.

Gessa, G., Melis, M., Muntoni, A., & Diana, M. (1998). Cannabinoids activate mesolimbic dopamine neurons by an action on cannabinoid CB1 receptors. *European journal of pharmacology*, 341(1), 39-44.

Goldstein, R. Z., & Volkow, N. D. (2011). Dysfunction of the prefrontal cortex in addiction: neuroimaging findings and clinical implications. *Nature reviews neuroscience*, 12(11), 652-669.

Gururajan, A., & Malone, D. T. (2016). Does cannabidiol have a role in the treatment of schizophrenia? *Schizophrenia research*, 176(2-3), 281-290.

Hahn, B. (2018). The potential of cannabidiol treatment for cannabis users with recent-onset psychosis. *Schizophrenia bulletin*, 44(1), 46-53.

Hanuš, L. O. (2009). Pharmacological and therapeutic secrets of plant and brain (endo) cannabinoids. *Medicinal research reviews*, 29(2), 213-271.

Henquet, C., Murray, R., Linszen, D., & van Os, J. (2005). The environment and schizophrenia: the role of cannabis use. *Schizophrenia bulletin*, 31(3), 608-612.

Hoffman, A. F., & Lupica, C. R. (2000). Mechanisms of Cannabinoid Inhibition of GABAASynaptic Transmission in the Hippocampus. *Journal of Neuroscience*, 20(7), 2470-2479.

Howes, O. D., & Kapur, S. (2009). The dopamine hypothesis of schizophrenia: version III—the final common pathway. *Schizophrenia bulletin*, 35(3), 549-562.

Howlett, A. C., Blume, L. C., & Dalton, G. D. (2010). CB1 cannabinoid receptors and their associated proteins. *Current medicinal chemistry*, 17(14), 1382-1393.

Hurst, D., Loeffler, G., & McLay, R. (2011). Psychosis associated with synthetic cannabinoid agonists: a case series. *American Journal of Psychiatry*, 168(10), 1119-1119.

Kapur, S., Mizrahi, R., & Li, M. (2005). From dopamine to salience to psychosis—linking biology, pharmacology and phenomenology of psychosis. *Schizophrenia research*, 79(1), 59-68.

Khantzian, E. J. (1997). The self-medication hypothesis of substance use disorders: A reconsideration and recent applications. *Harvard review of psychiatry*, 4(5), 231-244.

Kuepper, R., Morrison, P. D., van Os, J., Murray, R. M., Kenis, G., & Henquet, C. (2010). Does dopamine mediate the psychosis-inducing effects of cannabis? A review and integration of findings across disciplines. *Schizophrenia research*, 121(1-3), 107-117.

Leweke, F. M., Piomelli, D., Pahlisch, F., Muhl, D., Gerth, C. W., Hoyer, C., ... & Koethe, D. (2012). Cannabidiol enhances anandamide signaling and alleviates psychotic symptoms of schizophrenia. *Translational psychiatry*, 2(3), e94-e94.

Lupica, C. R., & Riegel, A. C. (2005). Endocannabinoid release from midbrain dopamine neurons: a potential substrate for cannabinoid receptor antagonist treatment of addiction. *Neuropharmacology*, 48(8), 1105-1116.

Lynch, M. R. (1992). Schizophrenia and the D1 receptor: focus on negative symptoms. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 16(6), 797-832.

Mackie, K. (2006). Mechanisms of CB1 receptor signaling: endocannabinoid modulation of synaptic strength. *International journal of obesity*, 30(1), 19-23.

Manini, A. F., Yiannoulos, G., Bergamaschi, M. M., Hernandez, S., Olmedo, R., Barnes, A. J., ... & Hurd, Y. L. (2015). Safety and pharmacokinetics of oral cannabidiol when administered concomitantly with intravenous fentanyl in humans. *Journal of addiction medicine*, 9(3), 204-210.

Marconi, A., Di Forti, M., Lewis, C. M., Murray, R. M., & Vassos, E. (2016). Meta-analysis of the association between the level of cannabis use and risk of psychosis. *Schizophrenia bulletin*, 42(5), 1262-1269.

Matsuda, L. A., Bonner, T. I., & Lolait, S. J. (1993). Localization of cannabinoid receptor mRNA in rat brain. *Journal of Comparative Neurology*, 327(4), 535-550.

Melis, M., Pistis, M., Perra, S., Muntoni, A. L., Pillolla, G., & Gessa, G. L. (2004). Endocannabinoids mediate presynaptic inhibition of glutamatergic transmission in rat ventral tegmental area dopamine neurons through activation of CB1 receptors. *Journal of Neuroscience*, 24(1), 53-62.

Meltzer, H. Y., & Stahl, S. M. (1976). The dopamine hypothesis of schizophrenia: a review. *Schizophrenia bulletin*, 2(1), 19-76.

Morales, P., & Reggio, P. H. (2019). CBD: a new hope? *CS Med. Chem. Lett,* 10(5), 694–695.

Morgan, C. J., & Curran, H. V. (2008). Effects of cannabidiol on schizophrenia-like symptoms in people who use cannabis. *The British Journal of Psychiatry*, 192(4), 306-307.

Morgan, C. J., Freeman, T. P., Powell, J. C. H. V., & Curran, H. V. (2016). AKT1 genotype moderates the acute psychotomimetic effects of naturalistically smoked cannabis in young cannabis smokers. *Translational psychiatry*, 6(2), e738-e738.

Morgan, C. J., Freeman, T. P., Schafer, G. L., & Curran, H. V. (2010). Cannabidiol attenuates the appetitive effects of Δ 9-tetrahydrocannabinol in humans smoking their chosen cannabis. *Neuropsychopharmacology*, 35(9), 1879-1885.

Müller-Vahl, K. R., & Emrich, H. M. (2008). Cannabis and schizophrenia: towards a cannabinoid hypothesis of schizophrenia. *Expert Review of Neurotherapeutics*, 8(7), 1037-1048.

Murray, R. M., & Di Forti, M. (2016). Cannabis and psychosis: what degree of proof do we require? *Biological psychiatry*, 79(7), 514-515.

Murray, R. M., Quigley, H., Quattrone, D., Englund, A., & Di Forti, M. (2016). Traditional marijuana, high-potency cannabis and synthetic cannabinoids: increasing risk for psychosis. *World Psychiatry*, 15(3), 195-204.

Newell, K. A., Deng, C., & Huang, X. F. (2006). Increased cannabinoid receptor density in the posterior cingulate cortex in schizophrenia. *Experimental Brain Research*, 172(4), 556-560.

Niesink, R. J., Rigter, S., Koeter, M. W., & Brunt, T. M. (2015). Potency trends of Δ9-tetrahydrocannabinol, cannabidiol and cannabinol in cannabis in the Netherlands: 2005–15. *Addiction*, 110(12), 1941-1950.

Nijenhuis, R. (2019). *Het ECS*. Retrieved on March 23, 2021 from https://www.canna-theek.com/blog/het-endocannabinoidesysteem/

Oleson, E. B., & Cheer, J. F. (2012). A brain on cannabinoids: the role of dopamine release in reward seeking. *Cold Spring Harbor perspectives in medicine*, 2(8), a012229.

Pearson, N. T., & Berry, J. H. (2019). Cannabis and psychosis through the lens of DSM-5. *International journal of environmental research and public health*, 16(21), 4149-4163.

Pierce, R. C., & Kumaresan, V. (2006). The mesolimbic dopamine system: the final common pathway for the reinforcing effect of drugs of abuse? *Neuroscience & biobehavioral reviews*, 30(2), 215-238.

Piomelli, D. (2008). Bedside to bench: The element of surprise. *Nature medicine*, 14(7), 720-721.

Potvin, S., Stip, E., & Roy, J. Y. (2003). Schizophrenia and addiction: An evaluation of the self-medication hypothesis. *L'encephale*, 29(3), 193-203.

Rijksoverheid (2021). *Gedoogbeleid softdrugs en coffeeshops*. Retrieved on March 22, 2021 from https://www.rijksoverheid.nl/onderwerpen/drugs/gedoogbeleid-softdrugs-en-coffeeshops

Room, R., Fischer, B., Hall, W., Reuter, P., & Lenton, S. (2010). *Cannabis policy: moving beyond stalemate*. Oxford: Oxford University Press.

Sarris, J., Sinclair, J., Karamacoska, D., Davidson, M., & Firth, J. (2020). Medicinal cannabis for psychiatric disorders: a clinically-focused systematic review. *BMC psychiatry*, 20(1), 1-14.

Schubart, C. D., Sommer, I. E., van Gastel, W. A., Goetgebuer, R. L., Kahn, R. S., & Boks, M. P. (2011). Cannabis with high cannabidiol content is associated with fewer psychotic experiences. *Schizophrenia research*, 130(1-3), 216-221.

Seely, K. A., Lapoint, J., Moran, J. H., & Fattore, L. (2012). Spice drugs are more than harmless herbal blends: a review of the pharmacology and toxicology of synthetic cannabinoids. *Progress in Neuro-psychopharmacology and biological psychiatry*, 39(2), 234-243.

Seltzer, E. S., Watters, A. K., MacKenzie, D., Granat, L. M., & Zhang, D. (2020). Cannabidiol (CBD) as a Promising Anti-Cancer Drug. *Cancers*, 12(11), 3203-3229.

Steen, R. G., Mull, C., Mcclure, R., Hamer, R. M., & Lieberman, J. A. (2006). Brain volume in first-episode schizophrenia: systematic review and meta-analysis of magnetic resonance imaging studies. *The British Journal of Psychiatry*, 188(6), 510-518.

Spanagel, R., & Weiss, F. (1999). The dopamine hypothesis of reward: past and current status. *Trends in neurosciences*, 22(11), 521-527.

Tanda, G., Pontieri, F. E., & Di Chiara, G. (1997). Cannabinoid and heroin activation of mesolimbic dopamine transmission by a common μ1 opioid receptor mechanism. *Science*, 276(5321), 2048-2050.

Tandon, R., Gaebel, W., Barch, D. M., Bustillo, J., Gur, R. E., Heckers, S., ... & Carpenter, W. (2013). Definition and description of schizophrenia in the DSM-5. *Schizophrenia research*, 150(1), 3-10.

Trimbos Instituut (2020). *THC-concentraties in wiet, nederwiet en hasj in Nederlandse coffeeshops 2019/2020*. Utrecht: Trimbos-instituut.

van der Stelt, M., & Di Marzo, V. (2003). The endocannabinoid system in the basal ganglia and in the mesolimbic reward system: implications for neurological and psychiatric disorders. *European journal of pharmacology*, 480(1-3), 133-150.

Van Os, J., Bak, M., Hanssen, M., Bijl, R. V., De Graaf, R., & Verdoux, H. (2002). Cannabis use and psychosis: a longitudinal population-based study. *American journal of epidemiology*, 156(4), 319-327.

Van Os, J., Rutten, B. P., & Poulton, R. (2008). Gene-environment interactions in schizophrenia: review of epidemiological findings and future directions. *Schizophrenia bulletin*, 34(6), 1066-1082.

Volkow, N. D., Baler, R. D., Compton, W. M., & Weiss, S. R. (2014). Adverse health effects of marijuana use. *New England Journal of Medicine*, 370(23), 2219-2227.

Wettenbank (2021*). Opiumwet*. Retrieved on March 22, 2021 from https://wetten.overheid.nl/BWBR0001941/2020-11-17

Wilson, R. I., & Nicoll, R. A. (2002). Endocannabinoid signaling in the brain. *Science*, 296(5568), 678-682.

Wise, R. A., & Bozarth, M. A. (1985). Brain mechanisms of drug reward and euphoria. *Psychiatric medicine*, 3(4), 445-460.

World Health Organization (2021). *Cannabis*. Retrieved on March 22, 2021 from https://www.who.int/teams/mental-health-and-substance-use/alcohol-drugs-and-addictive-behaviours/drugs-psychoactive/cannabis

Zavitsanou, K., Garrick, T., & Huang, X. F. (2004). Selective antagonist [3H] SR141716A binding to cannabinoid CB1 receptors is increased in the anterior cingulate cortex in schizophrenia. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 28(2), 355-360.

Zuardi, A. W. (2006). History of cannabis as a medicine: a review. *Brazilian Journal of Psychiatry*, 28(2), 153-157.

Zuardi, A. W., Morais, S. L., Guimaraes, F. S., & Mechoulam, R. (1995). Antipsychotic effect of cannabidiol. *The Journal of clinical psychiatry*, 56(10), 485–486

Zubin, J., & Spring, B. (1977). Vulnerability: a new view of schizophrenia. *Journal of abnormal psychology*, 86(2), 103-126.