U.PORTO

MESTRADO

MEDICINA LEGAL

Cannabis and Schizophrenia: Is there a link? A Systematic Review.

Ana Margarida Pina Águas

M

2021

U.PORTO

Ana Águas. Cannabis and Schizophrenia: Is there a link? A Systematic Review.

Cannabis and Schizophrenia: Is there a link? A Systematic Review.

Ana Margarida Pina Águas

INSTITUTO DE CIÊNCIAS BIOMÉDICAS ABEL SALAZAR

M.ICBAS **2021**

ANA MARGARIDA PINA ÁGUAS

CANNABIS AND SCHIZOPHRENIA: IS THERE A LINK? A SYSTEMATIC REVIEW

Dissertation for the Master's in Legal Medicine submitted to the Institute of Biomedical Sciences Abel Salazar (ICBAS), University of Porto

Supervisor: Diana Dias da Silva
Category: Researcher & Assistant Professor
Affiliations: Associate Laboratory i4HB – Institute for Health and Bioeconomy, UCIBIO – Applied Molecular Biosciences Unit, Laboratory of Toxicology, Department of Biological Sciences, Faculty of Pharmacy, University of Porto & TOXRUN – Toxicology Research Unit, University Institute of Health Sciences (IUCS), Department of Sciences, CESPU, CRL, Gandra

Co-Supervisor: Maria João Portugal Couto Valente
Category: Researcher & Invited Assistant
Affiliation: Associate Laboratory i4HB – Institute for Health and Bioeconomy, UCIBIO – Applied Molecular Biosciences Unit, Laboratory of Biochemistry, Department of Biological Sciences, Faculty of Pharmacy, University of Porto & Faculty of Pharmacy, University of Porto

Co-Supervisor: Maria José Carneiro de Sousa Pinto da Costa
Category: Invited Associate Professor
Affiliation: Institute of Biomedical Sciences Abel Salazar (ICBAS), University of Porto

INSTITUTO DE CIÊNCIAS BIOMÉDICAS ABEL SALAZAR
UNIVERSIDADE DO PORTO

Todas as correções determinadas
pelo júri, e só essas, foram efetuadas.

O Presidente do Júri,

Porto, _____/_____/_____

Acknowledgements

Já no fim deste percurso académico, não me posso esquecer de várias pessoas que me ajudaram imenso nesta etapa tão difícil. E como tal gostaria imenso de agradecer a ajuda e o apoio dessas pessoas.

Em primeiro lugar gostaria de agradecer imenso à Professora Doutora Diana Dias da Silva, pela excelente orientação e ajuda prestada ao longo desta Dissertação e mais do que tudo, pela sua disponibilidade. Pois mesmo quando estava muito ocupada, arranjava sempre um tempo para me ajudar no desenvolvimento deste tese.

À Professora Maria João Valente, por ter partilhado a sua experiência e ajuda no desenvolvimento desta dissertação, pois fez com que pudesse aprender imenso.

À Professora Doutora Maria José Pinto da Costa, Coordenadora do Mestrado em Medicina Legal, pela excelente orientação em todo o curso, pela preocupação que sempre demonstrou e pela simpatia.

A todos os professores do Mestrado em Medicina Legal pela experiência e pelos conhecimentos partilhados.

Às minhas colegas de curso, que nos tornamos muito facílmente amigas, pelo suporte mental e emocional prestado, pelos desabafos das nossas inseguranças em relação a este percurso, pela partilha de trabalhos, pelo esclarecimento de dúvidas académicas ou de procedimentos concursais e definitivamente pela camaradagem ao longo destes anos. Foi muito bom percorrer esta etapa convosco, meninas, OBRIGADA!

À minha Familia, em especial aos meus pais, por acreditarem em mim e nunca terem desistido de mim, mesmo quando eu própria já não acreditava e tinha desistido. Obrigada por me terem aturado em todo este percurso académico e por me ajudarem no percurso de ir ao Porto e vir para o Algarve, pois não teriam sido possíveis sem vocês. Por isso um muito obrigada.

Por último, mas definitivamente não menos importante quero agradecer aos meus meninos, o meu querido Pantufa, que infelizmente faleceu neste mês de julho com 18 anos e 9 meses, e a minha menina linda Luna pelo suporte emocional.

Um MUITO OBRIGADA a todos!

Abstract

The association between the use of Cannabis and the development of schizophrenia has been a heavily researched and debated topic for over three decades. Due to the high morbidity and mortality of schizophrenia, and to the extensive, widespread use of cannabinoids, it is important to clarify if Cannabis abuse is in fact a a component cause, or even a direct trigger, of the onset of this disease.

The present Dissertation aimed at conducting a systematic review of the available literature to determine the likelihood of an association of between the consumption of cannabinoid substances and the incidence of schizophrenia.

A thourough research of scientific publications was performed on multiple databases, including PubMed, Scielo, Science.gov, BMC, Cochrane, Google Scholar, and other relevant sources. A total of 6,328 published articles were found through specific combinations of keywords related Cannabis/cannabinoids and schizophrenia. After application of preestablished sets of inclusion and exclusion criteria, 58 studies were included in this systematic review.

The majority of the studies described a close association between Cannabis consumption and the onset of schizophrenia, or at least an increased risk of development of the disease. Some of these further showed a dose-response relationship. An association only in vulnerable individuals was described in 13 of these publications. Six studies found that Cannabis use was associated with an earlier onset of schizophrenia when compared to schizophrenic patients who had no consumption history. Only 5 out of 58 studies were not able to find any connection between Cannabis use and the development of schizophrenia.

Data from the analysed studies collectively support an involvement of Cannabis abuse in the onset of schizophrenia, which substantiates the need to raise public awareness about the consumption of cannabinoid substances. Nevertheless, further studies are essential to determine the precise role of Cannabis use on the development of this type of psychotic disorders, and the potential factors (genetic or environmental) influencing this association.

Resumo

A associação entre o uso de Canábis e o desenvolvimento da esquizofrenia tem sido um tema bastante investigado e debatido nas últimas três décadas. Devido à elevada morbilidade e mortalidade associada à esquizofrenia, e ao uso extensivo e generalizado de canabinóides, é importante esclarecer se o abuso de canábis é de facto um componente causal, ou até mesmo uma causa directa, do aparecimento desta doença.

A presente Dissertação visa a realização uma revisão sistemática da literatura disponível, com o objetivo de avaliar a probabilidade de existência uma associação entre o consumo de substâncias canabinóides e a incidência de esquizofrenia.

Foi realizada uma pesquisa de publicações científicas em múltiplas bases de dados, incluindo PubMed, Scielo, Science.gov, BMC, Cochrane, Google Scholar, e outras fontes relevantes. Um total de 6.328 artigos publicados foram encontrados através de combinações específicas de palavras-chave relacionadas com Canábis/canabinóides e esquizofrenia. Após a aplicação de conjunto de critérios de exclusão e inclusão pré-estabelecidos, 58 estudos foram incluídos nesta revisão sistemática.

A maioria dos estudos descreveram uma relação forte entre o consumo de Canábis e o início da esquizofrenia, ou pelo menos um risco acrescido de desenvolver a doença. Alguns destes estudos revelaram ainda uma relação dose-resposta. Uma associação, apenas em indivíduos vulneráveis foi descrita em 13 destas publicações. Seis estudos evidenciaram que o consumo de Canábis estava associado a um início precoce de esquizofrenia, quando comparado com pacientes esquizofrénicos que não tinham antecedentes de consumo. Apenas 5 dos 58 estudos não conseguiram estabelecer qualquer ligação entre o consumo de canábis e o desenvolvimento da esquizofrenia.

No seu conjunto, os dados dos estudos analisados apoiam um envolvimento do consumo de Canábis no início da esquizofrenia, o que comprova a necessidade de aumentar a consciência pública sobre o consumo de substâncias canabinóides. Apesar disso, são ainda necessários estudos adicionais para determinar o papel preciso do consumo de Canábis no desenvolvimento deste tipo de perturbações psicóticas, e os possíveis factores (genéticos ou ambientais) que influenciam esta associação.

List of abbreviations

Δ^9-THC – Delta-9-Tetrahydrocannabinol
2-AG – 2-Arachidonylglycerol
cAMP – Cyclic Adenosine Monophosphate
CARE – Cognitive Assessment and Risk Evaluation
CB1 – Cannabinoid Receptor 1
CB2 – Cannabinoid Receptor 2
CBD – Cannabidiol
CBN – Cannabinol
CI – Confidence Interval
CIP – Cannabis-induced Psychosis
CIPD – Cannabis-induced Psychosis Disorder
CNS – Central Nervous System
COMT – Catechol-*O*-Methyltransferase
DSM – Diagnostic and Statistical Manual of Mental Disorders
DSM-5 – Diagnostic and Statistical Manual of Mental Disorders, 5th edition
EC –Endocannabinoid
ECS –Endocannabinoid System
EMCDDA – European Monitoring Centre for Drugs and Drug Addiction
FAAH – Fatty Acid Amide Hydrolase
FEP – First-episode Psychosis
GABA – Gamma-Aminobutyric acid
HIV/AIDS – Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome
HR – Hazard Ratio
ICD – International Classification of Diseases
ICD-8 – International Classification of Diseases, 8th revision
ICD-10 – International Classification of Diseases, 10th revision
NMDA – N-Methyl-D-Aspartate
NS –Negative symptom
OR – Odds Ratio
PANSS – Positive and Negative Syndrome Scale
PNS – Peripheric Nervous System
PS – Positive symptom
PRISMA – Preferred Reporting Items for Systematic Reviews and Meta-Analyses
SC – Synthetic Cannabinoid

SCZ – Schizophrenia

SNP – Single Nucleotide Polymorphism

SSD – Schizophrenia Spectrum Disorder

Index

1 Introduction

1.1 Cannabinoids

Cannabinoids is a generic term used to describe a distinct group of terpenophenolic compounds that interact with cannabinoid receptors (Kim & Mahlberg, 1999). They can be differentiated into phytocannabinoids, which are the main botanical compounds of Cannabis and natural occurring cannabinoids that can be extracted from plants, especially Cannabis (Chicca et al., 2018; Zou & Kumar, 2018). Synthetic cannabinoid receptor agonists or more commonly known as synthetic cannabinoids (SCs), they have a synthetic or semisynthetic origin, that modulates one or more targets of the endocannabinoid system (ECS) (Giorgetti, Busardo, Tittarelli, Auwarter, & Giorgetti, 2020; Gurney, Scott, Kacinko, Presley, & Logan, 2014). And finally, the endocannabinoids (ECs), which are cannabinoids naturally produced by mammals, such as anandamide and 2-arachidonylglycerol (2-AG), belonging to the ECS (Degenhardt, Stehle, & Kayser, 2017; Maldonado, Banos, & Cabanero, 2016).

Phytocannabinoids and SCs are characterised for having a carbocyclic structure with 21 carbons and are generally formed by 3 rings, a cyclohexene, a tetrahydropyran, and a benzene (Barrales-Cureño et al., 2020). Their structure is normally assembled by 2 parts, the dihydroxyphenol (resorcin) carrying an alkyl chain, and a monoterpene moiety (Figure 1) (Degenhardt et al., 2017). Both phytocannabinoids and SCs interact with the ECS to produce the most prominent pharmacological effects, but also with other non-ECS pathways, producing desired and undesired effects (Brown et al., 2021; Zou & Kumar, 2018).

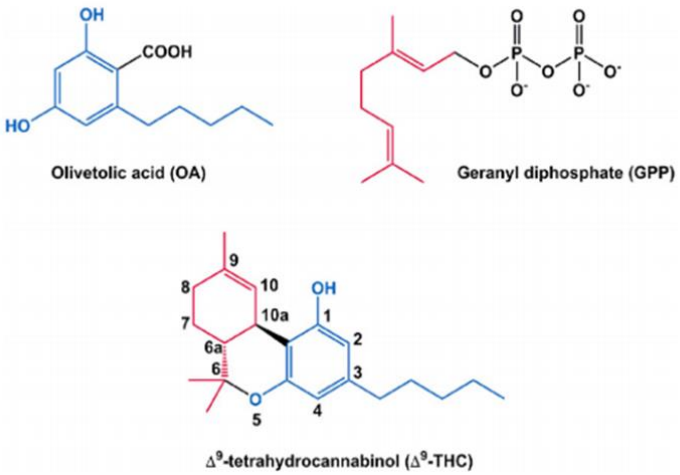

Figure 1 *General structure of cannabinoids and their precursors, olivetolic acid, and geranyl diphosphate. Cannabinoids are composed of two parts: a cyclic monoterpene part (red), and a diphenol (resorcin) part, carrying an alkyl chain (blue). The dibenzopyran-numbering system is used (Degenhardt et al., 2017).*

1.1.1 Endocannabinoids and the endocannabinoid system

The ECS, as shown in Figure 2, is a lipid-based signalling system of the brain composed by two major G protein-coupled receptors, namely the cannabinoid receptor 1 (CB1) and 2 (CB2), found in different cell types (Maldonado et al., 2016); by the ECs, such as anandamide and 2-AG , which are the endogenous, high affinity agonists of CB1 and CB2 (Baggelaar, Maccarrone, & van der Stelt, 2018; Cristino, Bisogno, & Di Marzo, 2020; Maldonado et al., 2016; Scherma et al., 2019); by a broader group of enzymes and transporters involved in the synthesis, degradation, and inactivation of ECs; and other molecular targets that compose the larger endocannabinoidome, which are lipids and specific receptors, whose main function is neuromodulation (Di Marzo V. & Wang J., 2014; Kokona, Tarricone, Di Forti, & Carra, 2017; Pazos, Nuñez, Benito, Tolón, & Romero, 2005; Pertwee et al., 2010), but are also involved in the control of many other functions, such as the immune response, appetite, gastrointestinal function, pain sensation, mood, differentiation and proliferation, and apoptosis of cells, and in processes of regulation such as fertility, pregnancy, pre- and post-natal development (Cristino et al., 2020; Kokona et al., 2017; Micale & Drago, 2018; Sharkey & Wiley, 2016).

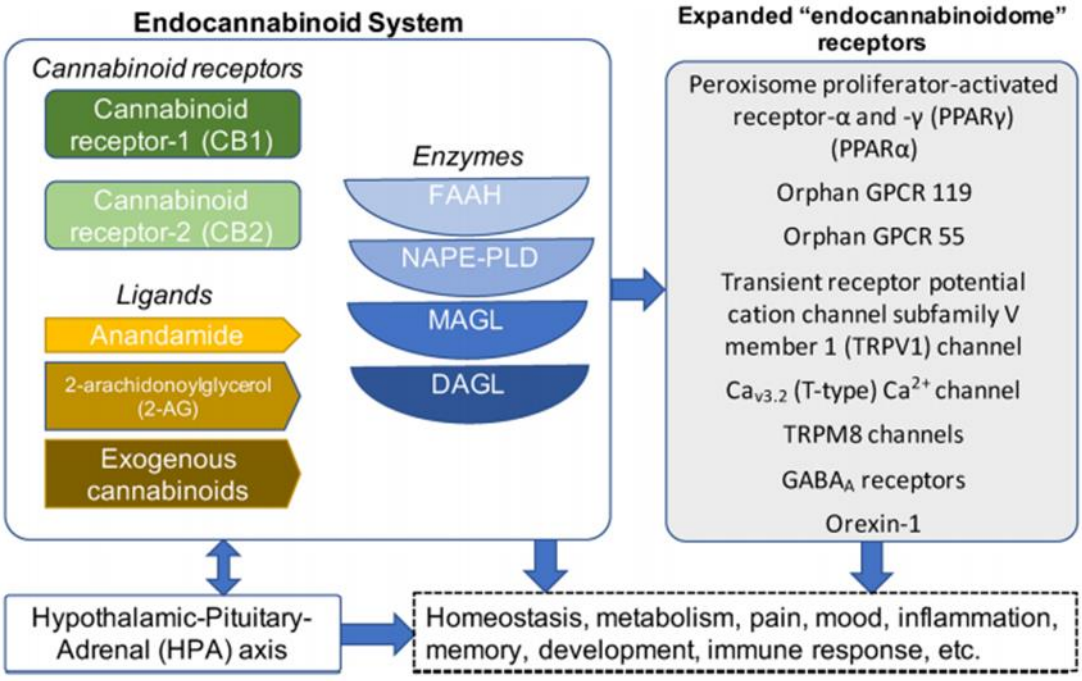

Figure 2 *Receptors, enzymes, and ligands that constitute the endocannabinoid system and the expanded endocannabinoidome. Complex interplays between these systems modulate many biological processes, conveying therapeutic benefits and adverse effects of Cannabis and cannabinoids. 2-AG; CB1; CB2; DAGL, diacylglycerol lipase; FAAH, fatty acid amide hydrolase; GABA, gammaaminobutyric acid; GPCR, G-protein coupled receptor; HPA; MAGL, monoacylglycerollipase; NAPE-PLD, N-acyl phosphatidylethanolamine phospholipase; PPARα; PPARγ; TRPM8, Transient receptor potential cation channel subfamily M (melastatin) member 8; TRPV1 (Brown et al., 2021).*

The ECs are endogenous lipid-based retrograde neurotransmitters that act presynaptically to inhibit the release of neurotransmitters on the terminals of neighbouring gamma-aminobutyric acid (GABA)-ergic and glutamatergic neurons (Kokona et al., 2017). As a consequence, they are involved in the regulation of cognitive functions in neuronal circuits of the cortex, memory in hippocampal neurons, emotions in neurons of the amygdala, motor activity in striatal projections neurons, in central processing of pain, and finally in the reinforcing effects of abuse substances in the mesolimbic system (Di Marzo, Bifulco, & De Petrocellis, 2004; Piomelli, 2003).

Anandamide is the major EC (Ramsay & Compton, 2011). It was the first to be identified as an endogenous ligand of the G protein-coupled CB1, and exhibits higher affinity towards CB1 than CB2 (Barnett-Norris et al., 2002). The anandamide-CB1 interactions result in the activation of the G proteins, particularly of the $G_{i/o}$ family (Barnett-Norris et al., 2002). Anandamide is not stored in cells, but formed when needed, being rapidly inactivated in the brain by enzymatic hydrolysis after receptor activation (Mechoulam & Hanuš, 2004).

The 2-AG is a EC that acts as an agonist of the CB1 and CB2, and it is an ester formed from omega-6-arachinodic acid and glycerol (National Center for Biotechnology

Information, 2021). This EC is an important modulator of oligodendrocyte functions in different physiopathological settings (Ilyasov, Milligan, Pharr, & Howlett, 2018).

As referred, CB1 and CB2 belong to a family of receptors coupled to the G proteins, specifically the inhibitory type, and their activation is directly involved in the control of the GABAergic and glutamatergic neurotransmission (mediated by CB1), and in the modulation of the immune system and neuroinflammation (mediated by CB2) (Barrales-Cureño et al., 2020; Kaur, Ambwani, & Singh, 2016; Lupica & Riegel, 2005; Melis et al., 2004; Scherma et al., 2019; Zou & Kumar, 2018).

CB1 is generally a "neuronal" receptor (Norrod & Puffenbarger, 2007). It was first described in 1988 by Devane, Dysarz, Johnson, Melvin, and Howlett (1988), and is a 7 segment transmembrane protein that is encoded by the gene *CNR1* and composed by 472 amino acids in humans (Howlett, 1998; Zou & Kumar, 2018). This receptor is especially located on the presynaptic axons and nerve terminals and maintains homeostasis by preventing excessive or insufficient release of diverse neurotransmitters such as dopamine, norepinephrine, glutamate, GABA, and serotonin, by presynaptic regulation (Gareeva et al., 2020; Ishac et al., 1996; Ramsay & Compton, 2011). CB1 is highly expressed in the central nervous system (CNS), specifically in the nuclei of the hippocampus, the cerebral cortex (especially frontal regions), the limbic forebrain (particularly in the hypothalamus and anterior cingulate cortex), the thalamus, the cerebellum, the basal ganglia (striatum, globus pallidus, and substantia nigra), and the periaqueductal grey matter (Figure 3), making it the most widely expressed receptor in the brain (Cristino et al., 2020; Davis, 2014; Iversen, 2004; Kaur et al., 2016; Zou & Kumar, 2018). These localizations of CB1 in the CNS are closely related to the majority of cannabinoid effects including modulation of the cognitive function, pain, short-term memory, motor control and coordination, hypothermia and hyperphagia (Bonfa, Vinagre, & de Figueiredo, 2008). CB1 also has high expression in the peripheral nervous system (PNS), especially in the sympathetic nerve terminals, dorsal root ganglia and dermic nerve ending, and it is less expressed in testis, immune system, adrenal glands, bone marrow, heart, blood vessels, lungs, prostate, thymus, tonsils, and spleen (Figure 3) (Bouaboula et al., 1993; Galiegue, Mary, Marchand, & al., 1995; Hampson, Grimaldi, Axelrod, & Wink, 1998; Harvey, N.A.; Pertwee, 1997; Veress et al., 2013). The activation of CB1 might lead to a subsequent inhibition of adenylate cyclase, initiating depletion of intracellular cAMP that results in reduction of protein kinase A activity. On the other hand, some studies have also reported that CB1 might stimulate adenylate cyclase, thereby being able to increase intracellular cAMP levels (Di Marzo, 2008). Additionally, the CB1 is also able to control ion channels in the neuronal cell membrane: upon G protein-coupled activation, cannabinoids may positively influence inwardly rectifying potassium currents in a βγ-subunit-mediated

manner, resulting in an elevated resting potential in neurons (Guo & Ikeda, 2004; Henry & Chavkin, 1995). Besides, the neuronal calcium channels can also be inhibited by cannabinoids in the same manner (Guo & Ikeda, 2004). Since the CB1 expression in neurons is largely restricted to presynaptic terminals, the effects of cannabinoids on these ion channels suggest a important role in modulating presynaptic functions and consequent neurotransmitter release (Katona & Freund, 2008).

By its turn, CB2 is known as an “immune system” receptor (Norrod & Puffenbarger, 2007), being mainly expressed in the periphery where it has been shown to produce immunomodulating effects with anti-inflammatory action (Brown et al., 2021; Gareeva et al., 2020). It has a 68% nucleotide homology with CB1 within the transmembrane regions (Berdyshev, Boichot, & Lagente, 1996), and 44% sequence homology at the protein level (Zou & Kumar, 2018). The CB2 is encoded by the gene *CNR2*, and consists of 360 amino acids in humans (Zou & Kumar, 2018). Its activation is also involved in the modulation of adenylate cyclase, but does not inhibit the calcium channels or overstimulates the output of potassium (Netzahualcoyotzi-Piedra, Muñoz-Arenas, Martínez-García, Florán-Garduño, & Limón-Pérez de León, 2009). This receptor is highly expressed in the immune cells (myeloid and erythroid cells, macrophages, mast cells, circulating leukocytes and T and B lymphocytes) of lymphoid organs, such as the spleen, thymus, tonsils, bone marrow and pancreas (Howlett et al., 2002; Pertwee, 1997); and moderately expressed in other peripheral tissues, like the liver, adipose tissue, bone, and cardiovascular or reproductive systems (Zou & Kumar, 2018); it is also expressed in the CNS (in microglia) (Núñez et al., 2008), in which it associates directly with the neuroinflammation processes (Lunn et al., 2006). So, although CB1 and CB2 are expressed in CNS, only the CB1 is present in the PNS and responsible for altering neurotransmitter release and sensory perception (Castaneto et al., 2014).

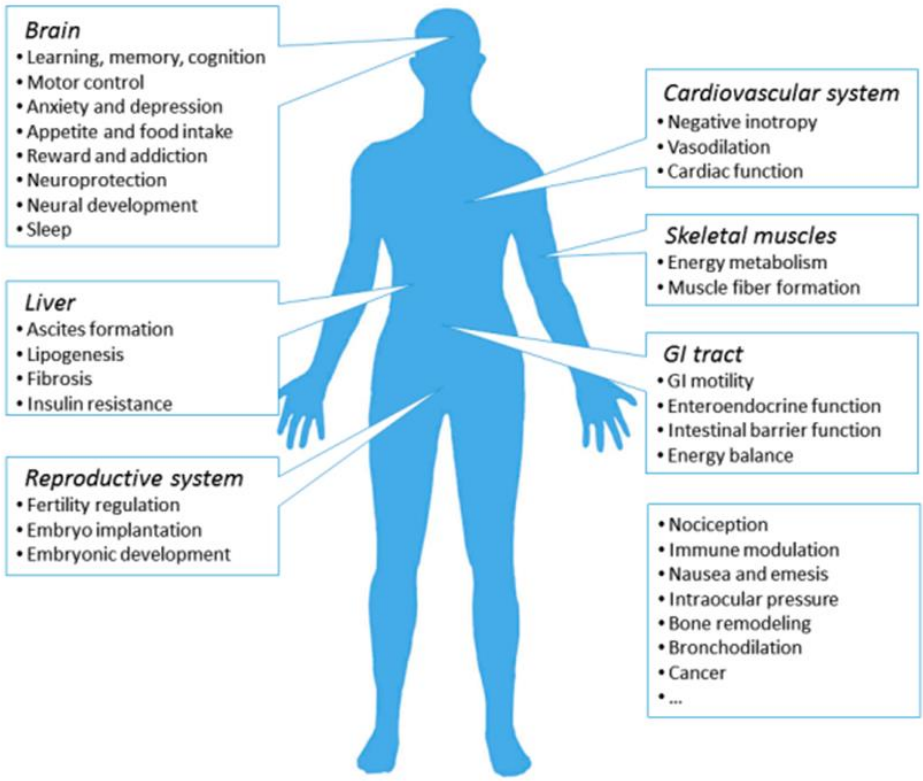

Figure 3 *Major localization sites and associated functions of the CB1 in the human body. In the brain, CB1 is involved in many neurological activities; in peripheral sites, CB1 regulates the local tissue functions, although to a lesser extent (Zou & Kumar, 2018).*

Overall, the release of ECs requires the enzymatic cleavage of phospholipid precursors present in the membranes of neurons and other cells. Once released, ECs activate the cannabinoid receptors on nearby cells and are rapidly inactivated by active reuptake by neurons and subsequent enzymatic hydrolysis by fatty acid amide hydrolase (FAAH) (an enzyme that hydrolysis anandamide (Ramsay & Compton, 2011)) (Piomelli, Giuffrida, Calignano, & Rodriguez de Fonseca, 2000). At the presynaptic nerve terminal, the activation of the CB1 by the ECs will lead to a decrease in the membrane permeability to calcium and potassium, and a decrease in the activity of adenylate cyclase, thus inhibiting the release of glutamate, dopamine, acetylcholine and noradrenaline (Wobrock, Czesnik, & Malchow, 2011). So, in the end, the ECS works as a retrograde messenger system tuning and regulating the potential hyper- and hypoactivation of the neurotransmitter systems mentioned above (Wobrock et al., 2011).

1.1.2 Cannabis and phytocannabinoids

Cannabis is the most used psychoactive substance in the world (EMCCDA, 2021; Ramsay & Compton, 2011; World Drug Report, 2021a, 2021b), its prevalence being

around 5 times over that of other drugs (EMCDDA, 2021). There were an estimated 200 million past-year users of Cannabis in 2019, corresponding to 4.0% of the global population aged 15–64, and 14 million past-year users of Cannabis among students aged 15–16 (World Drug Report, 2021a). The annual prevalence of the use of Cannabis remains the highest in North America, Australia and New Zealand (12.1%), and West and Central Africa (9.4%) (World Drug Report, 2021b). Cannabis was also the most common drug reported by the European Drug Emergencies Network in 2019 (EMCDDA, 2021), being also the most common substance that European people try (47.6 million males and 30.9 million females) (EMCDDA, 2021). Last year, in Europe, 22.2 million (7.7%) adults and 15.8 million (15.4%) young adults (aged 15-34) used Cannabis (EMCDDA, 2021). The mean age for users was 17 years, the majority being male users, the mean use was 5.2 days a week, and 49% used it daily (EMCDDA, 2021). The resin of Cannabis sold in Europe is currently more potent than in the past, with delta-9-tetrahydrocannabinol (Δ^9-THC) content on average ranging between 20-28%, almost twice that of the herbal one (8-13%) (EMCDDA, 2021). Over the past decade, an increasing number of Cannabis products with high potency have been introduced to the Cannabis market. These products tend to be high in Δ^9-THC and low in cannabidiol (CBD) (World Drug Report, 2021a).

The taxonomic classification of the Cannabis plant, more precisely *Cannabis Sativa spp.*, is presented in Figure 4 (ElSohly, Radwan, Gul, Chandra, & Galal, 2017). Cannabis is a dioecious plant species, which means that it has 2 separate genders (stem male and stem female) (Figures 5 (Farag & Kayser, 2017; Netzahualcoyotzi-Piedra et al., 2009). This plant is typical of temperate zones, although its cultivation is widespread as it is very resistant and tolerates well climate changes. Cannabis height is around between 1.6 to 6 meters (Farag & Kayser, 2017), with the female being more durable and leafier (Netzahualcoyotzi-Piedra et al., 2009).

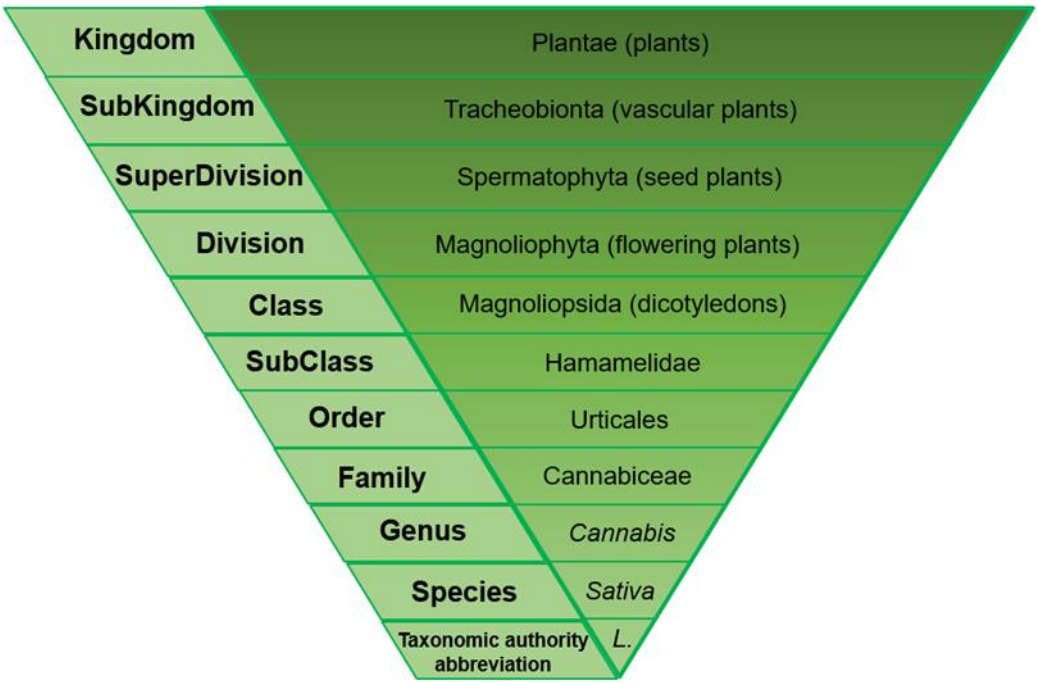

Figure 4 *The Taxonomic classification of Cannabis sativa (ElSohly et al., 2017).*

Figure 5 *Differentiation between male stem and female stem in Cannabis sativa spp.. Retrieved from: https://www.alchimiaweb.com/blogen/distinguish-marijuana-males-females/ and https://dutch-passion.com/en/blog/sexing-cannabis-how-to-tell-if-your-plant-is-male-or-female-n988. Accessed: 20 of June of 2021.*

The Cannabis leaves are arranged in the shape of palm, with about 5-7 leaves per palm, the biggest being located in the centre. The male plant has a head in the flower that produces pollen, while the flowers of the female plant are much smaller (Netzahualcoyotzi-Piedra et al., 2009). The male plant dies slightly after spreading the pollen, whilst the female survives to maturity of the seeds (Netzahualcoyotzi-Piedra et al., 2009). The phytocannabinoids are present in all parts of the plant except the seeds (van Bakel et al., 2011), they are highly concentrated in the resin (or hashish) produced by the glands of the base of the thin layer of villi in the leaf, particularly in the bracts of the heads in the female plant flower (Netzahualcoyotzi-Piedra et al., 2009).

Besides phytocannabinoids, Cannabis is constituted by terpenes, alkaloids, amides, flavonoids, fatty acids, and non-cannabinoid phenols (ElSohly et al., 2017; Elsohly & Slade, 2005), as shown in the Figure 7. Quite a few of these compounds are responsible for the colour and unique smell of Cannabis and might have further pharmacological effects or even modulate the pharmacological effects of the cannabinoids (ElSohly et al., 2017; Elsohly & Slade, 2005). As of 2015, 565 compounds have been identified, more than 100 are phytocannabinoids (ElSohly et al., 2017; Elsohly & Slade, 2005), with the most abundant ones being the Δ^9-THC, cannabinol (CBN), and CBD (Elsohly & Slade, 2005; Netzahualcoyotzi-Piedra et al., 2009). The 2 main phytocannabinoids found in Cannabis (Δ^9-THC and CBD) have opposite effects: while the Δ^9-THC is psychotomimetic, CBD has antipsychotic properties (Morgan & Curran, 2008).

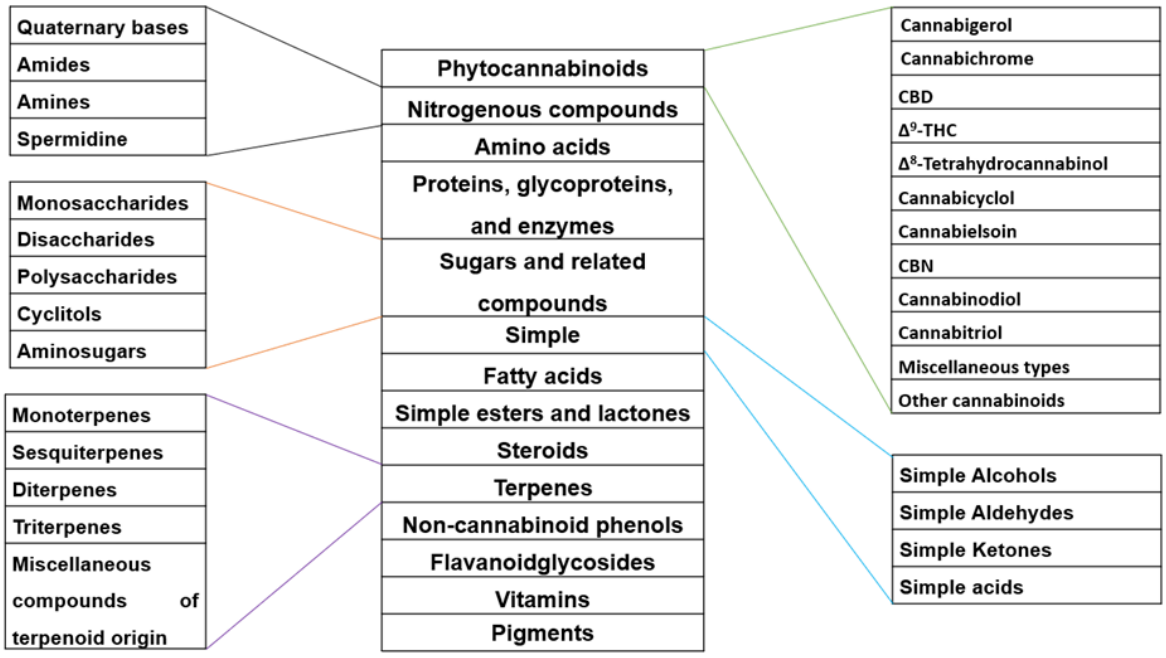

Figure 6 *Classes of chemicals constituents of Cannabis sativa L.. CBD; Δ^9-THC; Δ^8- Tetrahydrocannabinol, Delta-8-Tetrahydrocannabinol; CBN (Elsohly & Slade, 2005).*

Δ^9-THC is the most abundant psychoactive constituent of the plant Cannabis and was first discovered in the 1960s, but its biological targets were only discovered in the 1980s (Honorio et al., 2010). Similar to the other cannabinoids, (Zuurman, 2008)it displays lipophilic properties, being easily absorbable and, which consequently speeds the onset of effects (Mechoulam, Devane, & Glaser, 1992). The main effect Δ^9-THC produces is euphoria, which depends on the concentration and speed at which it is absorbed, which in turn depends on the route of administration (Ramsay & Compton, 2011). Besides the euphoric effect, commonly known as "high", Δ^9-THC consumption can also result in at least two well-defined psychological state changes, namely the derealization of self and surroundings and an anxious/depressive state (Dittrich & Woggon, 1972). It can also result in perceptual changes, for example, colours become brighter, the music becomes more vivid, and time appears to go faster (Ashton, 2001). Its consumption can also increase diastolic blood pressure and heart rate, decrease body temperature, increased expired carbon monoxide, and after chronic consumption, the individual present respiratory problems and reduced lung tissue density (Aldington et al., 2007; Cooper & Haney, 2009; Dittrich & Woggon, 1972).

CBD is the second most abundant constituent of Cannabis, and it has been of great interest due to its anxiolytic and antipsychotic properties (Ramsay & Compton, 2011). Due to the lack of psychoactive properties, CBD opened opportunities for its medical use, without dose-limiting side effects (Ibeas Bih et al., 2015; Netzahualcoyotzi-Piedra et al., 2009). A few studies suggest that CBD attenuates Δ^9-THC effects, like anxiety, cognitive deficits and psychosis (Boggs, Nguyen, Morgenson, Taffe, & Ranganathan, 2018). Likewise, it has a neuroprotective role by acting as an antioxidant against oxidative stress produced in neurons by excessive glutamate release (Hampson et al., 1998). This compound is a weak partial antagonist of CB1 and inhibits the reuptake and hydrolysis of anandamide, displaying pharmacological actions such as anti-convulsive, sedative, hypnotic, anti-inflammatory, neuroprotective and antipsychotic (Roser, Vollenweider, & Kawohl, 2010; Scuderi et al., 2009). Without significant intrinsic activity on cannabinoid receptors, CBD might be an inverse agonist of CB2, which has implications for the immune system, including anti-inflammatory effects (Pisanti et al., 2017). Due to its therapeutic potential, it is commercially available as tinctures and oils, infused in lip balms, vaporizers, edibles, topicals, essential oils, and pet food (Brown et al., 2021).

By its turn, CBN is a phytocannabinoid that is also a degradation product of Δ^9-THC, being found in larger quantities in dried products (De Petrocellis et al., 2011). This cannabinoid also has psychoactive properties, but much lower than Δ^9-THC. CBN has also more affinity for the CB2, compared to CB1 (Netzahualcoyotzi-Piedra et al., 2009). Its

action on CB2 on the splenocytes (macrophages of the spleen) and thymocytes (macrophages of the thymus) is to inhibit adenylate cyclase and reduce the activity of the protein kinase A and transcription factors dependent on cAMP, leading to a decrease in the transcription of the gene for interleukin-2 that participates in the regulation of the system, which, among others, might explain the capacity of immunomodulation attributed to Cannabis (Condie, Herring, Koh, Lee, & Kaminski, 1996).

The use of Cannabis either medically or recreationally is very controversial, with many supporters and opponents. Although Cannabis abuse may cause adverse effects, it appears to also have many benefits in diverse pathologies, including end-stage cancer, sclerosis (amyotrophic lateral sclerosis and multiple sclerosis), seizure disorders, Crohn's disease, mitochondrial diseases, sickle cell disease, debilitating epileptic conditions, life-threatening seizures, wasting syndrome and chronic pain (World Drug Report, 2021b). It can also be used in the treatment of chemotherapy-induced nausea and vomiting, in motor disorders associated with neurodegenerative diseases, such as Huntington and Parkinson's disease, in mental disorders, like Sleep Disorder, Post Traumatic Stress Disorder, and anxiety, in treatment of glaucoma and dystonia, as well as an appetite inducer and decreasing weight loss associated with HIV/AIDS (National Academies of Sciences Engineering and Medicine, 2017).

As a consequence, by virtue of the plethora of distinct pharmacological actions attributed to Cannabis constituents, the plant products are used/or advocated to be used as hypnotic agents, analgesics, antiasthmatics, antihypertensives, immunomodulatory, anti-inflammatory, or neuroprotective and antiepileptic drugs, spasticity, motor and eating disorders, and even neurogenerative diseases, like Alzheimer's and Parkinson's (Svíženská, Dubový, & Šulcová, 2008).

On the other hand, there is much evidence that the consumption of Cannabis can cause adverse effects that can remain for days, weeks, months, and even years (Hall & Solowij, 1998). The effects of Cannabis use can be divided into short and long-term (Vindenes & Mørland, 2017), and many of the acute effects had a dose-response relationship (Heishman, Stitzer, & Yingling, 1989).

The short-term effects are normally the cognitive impairment/deterioration (affects the memory, learning, attention/time perception, and information processing), psychomotor impairment (affects the react time, the divided attention, and the driving skills), and paranoia or psychotomimetic effects (e.g., those measured by the PANSS (Positive and Negative Syndrome Scale)) (Hall & Solowij, 1998; Vindenes & Mørland, 2017). These psychotomimetic effects will depend on the strain of the plant, the part of the plant ingested, the proportional content of Δ^9-THC in the plant, the dose consumed, the type of preparation, the route of administration, the personality of the consumer, and the

cultural and social background, but the typical euphoric effects tend to be consistent (Castle & Solowij, 2004; Netzahualcoyotzi-Piedra et al., 2009).

The long-term use of Δ^9-THC might increase the risk of neuropsychiatric disorders later in life and result in poorer brain development (Dharmapuri, Miller, & Klein, 2020). These effects can be cognitive impairment (downregulation of receptors, which produces activity in different brain regions, altered brain development, learning deficit and reduction in the intelligence coefficient), psychosis (several psychoactive effects that are similar signs and symptoms of schizophrenia (SCZ)) and related psychotic disorders, which are group of serious mental illnesses, and addiction, which can lead to Cannabis use disorder, also known as Cannabis abuse/dependence (American Psychiatric Association, 2013; Casarella, 2020; Ramsay & Compton, 2011; Vindenes & Mørland, 2017). .

1.1.3 Synthetic cannabinoids

SCs comprise a wide range of chemically dissimilar man-made substances that have the common feature of acting on CB1 and CB2 (World Drug Report, 2021a). Many were originally developed for therapeutic purposes or as probes for the ECS (Tamba et al., 2020), but in the last decades they resurged in the drug markets for recreational purposes. Either used as pure substances or blended in herbal mixtures marketed as “Spice”, “K2”, “fake weed”, and “legal highs” (Seely, Lapoint, Moran, & Fattore, 2012; World Drug Report, 2021a), SCs are now the most commonly used new psychoactive substances (World Drug Report, 2021a), with their consumption being associated to greater abuse potential and more severe toxic effects than Δ^9-THC (Diao & Huestis, 2019; Seely et al., 2012; Vemuri & Makriyannis, 2015).

Chemically, they are very difficult to categorise because the group is comprised of several compounds with highly distinct structures, and many new molecules keep appearing in the drug markets all the time to avoid legal ramifications (Krotulski, Cannaert, Stove, & Logan, 2021; Mills, Yepes, & Nugent, 2015; Potts, Cano, Thomas, & Hill, 2020; Seely et al., 2012). Nevertheless, in general, they are lipid-soluble, nonpolar, and highly volatilised drugs (Gurney et al., 2014; Mills et al., 2015; Seely et al., 2012).

SCs can also activate or inhibit the ECS directly or indirectly in the CNS and periphery (Brown et al., 2021), having affinity and acting as agonists of one or both cannabinoid receptors. There is also evidence that they interact with other receptors, such as vanilloid or serotonergic receptors (Morales, Hurst, & Reggio, 2017; Pertwee, 2008).

SCs use grown rapidly since the 2000’s, such that, in 2018, 0.5% of England and Wales adult population reported to have used NPS, which were mainly SCs (World Drug

Report, 2021a), while in Egypt the use of SCs ("Strox") was reported to be 6.8% among university students. In 2019, 2.5% of adolescents in 32 countries in Europe reported the use of NPS at least once that year, the majority also being SCs. The highest prevalence was observed in Monaco, Poland, Estonia, Latvia and Czechia (4.0-4.9%), while the lowest was reported in North Macedonia, Finland and Portugal (0.4-0.8%) (World Drug Report, 2021a). On a positive note, there has been a decrease in the number of new SCs appearing on the market in recent years. Nevertheless, SCs have one of the highest number of seizures amongst all NPS groups, and their abuse is still responsible for a large percentage of NPS-related intoxication cases (about 8.7% between January, 2019 and April, 2020) (EMCDDA, 2021; World Drug Report, 2021a).

Europe is reported to produce both Cannabis and SCs. While Cannabis is mostly for internal consumption, the synthetic drugs are manufactured both for the European market and exported to other countries (EMCDDA, 2021). There are also reports that Cannabis has been adulterated with new SCs and being sold to unsuspecting users (EMCDDA, 2021).

There are continuously new potent SCs emerging, which poses a major health and social threat. For instance, the changes to the basic structure of Δ^9-THC (e.g., the lengthening of the alkyl side chain, which enhances the selectivity and affinity to the receptors), is a starting point for the development of SCs (Bow & Rimoldi, 2016; Prandi, Blangetti, Namdar, & Koltai, 2018). The best-known family of SCs is named "JWH", after John W. Huffman, being the main compounds in Spice/K2 products. Chemically, they are aminoalkylindoles (Tamba et al., 2020), as seen in Table 1 with more than 60 known compounds so far (Schlatter & Atta, 2014). The JWH-018 was one of the first SCs to appear in the drug markets (World Drug Report, 2021a). It is the only SC, to date, to have been studied in controlled clinical trials (Theunissen et al., 2021), and it is very popular because it has a strong pharmacological effect, is easily synthesized, and used as a precursor of other SCs with varying characteristics and affinity towards cannabinoid receptors (Banister et al., 2015; Schlatter & Atta, 2014). There are two other very well-known groups, namely the classical cannabinoids HU (Hebrew University) and the CP (cannabimetics), the later one was originally developed by Pfizer in 1970 (Banister et al., 2015; Schlatter & Atta, 2014). The HU-210 was the first to be synthesized in Israel in 1988, and it is almost identical to the structure of Δ^9-THC, although 100 times more potent, but contrary to JWH-018 it is challenging to synthetize, and it is thus not commonly detected in the products appearing in the illicit market (Banister et al., 2015; Schlatter & Atta, 2014; World Drug Report, 2021a). Other potent SCs are JWH-018, JWH-250, and JWH-081 (World Drug Report, 2021a). There are also new SCs with indazole-based structure, such as 5F-ADB (5F-MDMB-PINACA), which was the most common SCs

identified by US Drug Enforcement Agency seizures in 2016 (Krotulski et al., 2021). Currently, the most popular SCs circulating through the markets are the HU-210, JWH-018, JWH-073, JWH-250, JWH-081, MDMB-CHMICA, AMB-FUBINACA, MDMB-4en-PINACA and 4F-MDMB-BICA (EMCDDA, 2021; World Drug Report, 2021a). There was a total of 209 new SCs detected in Europe since 2008, including 11 for the first time in 2020 (EMCDDA, 2021). Many of these SCs are considered illegal or are controlled substances in many countries, especially in Europe, USA, Australia, New Zealand, and China.

Table 1 *Classification of the synthetic cannabinoids, the year of their appearance, number of reported deaths, and countries were they are currently banned or controlled.*

SC Classes		Representatives	Year of Identification	Number of Deaths	Countries were it is Banned or is a Controlled Substance
Aminoalkylindones	Nathphoylindones	JWH-018	2008 (on the market)	About 60 deaths	Australia, China, Ireland, Jordan, Sweden, Canada, Germany, UK, USA, Austria, Turkey, Belarus, Estonia, France, Finland, Italy, Japan, Latvia, New Zealand, Norway, Poland, Romania, Russia, South Korea, Ukraine, Switzerland, Luxembourg, and Brazil
		JWH-073	2009	No deaths reported	Canada, Germany, UK, USA, Latvia, Australia, New Zealand, Turkey, and Poland
		JWH-081	2010	No deaths reported	Canada, Germany, UK, USA, China, and Poland
		AM-2201	2011	At least 3 deaths	USA, Canada, Germany, UK, and New Zealand
		MAM-2201	2011	At least 1 death	USA, New Zealand, China, UK, Germany, and Canada
	Phenylacetyl indoles	JWH-250	2009	No deaths reported	Australia, Canada, Germany, UK, USA, Czechia, Latvia
Indazole-3-carbomaxide		5F-ADB (5F-MDMB-PINACA)	2014	Associated with 35 deaths	USA, Japan, Canada, Germany, and UK
Indazole-based compound		AMB-FUBINACA	Made by Pfizer in 2009	At least 60 deaths	USA, Sweden, Canada, Germany, New Zealand and UK
Indole-based		MDMB-4en-PINACA	2018	At least 9 deaths	Sweden, Canada, Germany, UK
Indole-based		MDMB-CHMICA	2014	At least 29 deaths	USA, Austria, Canada, China, Croatia, Denmark, Estonia, Finland, Germany, Greece, Hungary, Latvia, Lithuania, Luxembourg, Norway, Portugal, Turkey, UK, Sweden, Switzerland, Europe Union, Brazil, and Poland
Dibenzopyrans		HU-210	Made in 1988	No deaths reported	Canada, UK, USA, New Zealand, UNODC (United Nation Office on Drugs and Crime)
Dimethyl butanoate		4F-MDMB-BICA	2020	21 deaths	Europe Union, Ireland, Denmark,

4F-MDMB-BICA – methyl 2-({[1-(4-fluorobutyl)-1H-indol-3-yl]carbonyl}amino)-3,3-dimethylbutanoate; 5F-ADB (5F-MDMB-PINACA) – N-[[1-(5-fluoropentyl)-1H-indazol-3-yl]carbonyl]-3-methyl-D-valine methyl ester; AM-2201 – 1-(5-fluoropentyl)-3-(1-naphthoyl)indole; AMB-FUBINACA – methyl 2-(1-(4-fluorobenzyl)-1H-indazole-3-carboxamido)-3-methylbutanoate; HU-210 – (6aR,10aR)-9-(Hydroxymethyl)-6,6-dimethyl-3-(2-methyloctan-2-yl)-6a,7,10,10a-tetrahydrobenzo[c]chromen-1-ol; JWH-018 – 1-pentyl-3-(1-naphthoyl)indole; JWH-073 – 1-Butyl-3-(1-naphthoyl)indole; JWH-81 – (4-Methoxynaphthalen-1-yl)(1-pentylindol-3-yl)methanone; JWH-250 – 1-pentyl-3-(2-methoxyphenylacetyl)indole; MAM-2201 – [1-(5-fluoropentyl)-1H-indol-3-yl](4-methyl-1-naphthalenyl)-methanone; MDMB-4en-PINACA – methyl 3,3-dimethyl-2-(1-(pent-4-en-1-yl)-1H-indazole-3-carboxamido)butanoate; MDMB-CHMICA – methyl 2-[[1-(cyclohexylmethyl)indole-3-carbonyl]amino]-3,3-dimethylbutanoate; SC – Synthetic Cannabinoids; UK – United Kingdom; USA – United States of America.

SCs produce effects like Δ^9-THC, but much more potent by virtue of the stronger efficacy and higher affinity for the CB1 (Mills et al., 2015; Prandi et al., 2018). As such, they also cause more severe neuropsychiatric manifestations and sympathomimetic-cardiac toxic effects, like seizures, loss of consciousness, severe hallucinations, psychosis, vomiting, drowsiness, chest pain, agitation, hot flushes, dilation of pupils, dry mouth, anxiety, suicide ideation, self-harm, strokes and heart attacks, anti-nociception, concentration problems, changed perception, and acute memory impairment, often

leading to hospitalization and death (Bulbena-Cabre, DiGenova, Sigel, Dunn, & Swift, 2018; Kaló, Kassai, Rácz, & Van Hout, 2018; Mills et al., 2015; Moeller et al., 2017; Muller, Kornhuber, & Sperling, 2016; Nurmedov et al., 2015; Spaderna, Addy, & D'Souza, 2013; World Drug Report, 2021a). Of note, 33 cases of AMB-FUBINACA-related intoxication were reported in 2016 in New York City; Turkey reported 300 deaths caused by the use of SCs in 2018, the majority with JWH-018 (World Drug Report, 2021a); while 21 deaths associated with the SC MDMB-4en-PINACA and 4F-MDBM-BICA were reported in 2020 in Hungary (EMCDDA, 2021).

Although the majority of the SCs have adverse effects, some of them are used therapeutically. Nabilone is one of them, imitating the Δ^9-THC actions to treat pain, chemotherapy-induced nausea and vomiting, and anorexia and weight loss in HIV/AIDS (Brown et al., 2021).

1.2 Schizophrenia

SCZ is a chronic, severe, and often progressive disabling mental disorder (Nielsen, 2011), that affects millions of people globally (World Health Organization, 2019). Data from the Global Burden of Disease Study 2016 (Charlson et al., 2018) reported around 20.9 million prevalent cases of SCZ that year, with an estimated global prevalence of 0.28%. This disease is characterized by positive, negative and mood symptoms, impaired capacity for coping, elevated distress and a significant decline in cognition, quality of life and psychological functioning (Ritsner & Lerner, 2011). SCZ has a variable phenotypic expression, which is poorly understood, and a complex etiology that involves a major genetic contribution, with multiple genes and different combinations of their polymorphic variants, as well as environmental factors interacting with the genetic susceptibility (Jablensky, 2010). It is agreed that the glutamate deficit is probably the key contributor to the pathophysiology of SCZ since it is thought to lie in the inhibitory control of glutamatergic neurotransmission, resulting in pathological neuronal excitability (Mortimer, 2011). There is also the N-Methyl-D-Aspartate (NMDA) receptor that inhibits the glutaminergic neurotransmission, making the NMDA antagonists evoke SCZ-like symptoms in healthy volunteers (Mortimer, 2011).

The psychotic features of SCZ usually appear between the late adolescence and mid-30s, while its appearance before adolescence is rare. On the other hand, the peak age of onset of the first psychotic episode is between the beginning and mid-20s for males and late 20s for females (American Psychiatric Association, 2013).

The decreasing of psychotic symptoms throughout life might be associated with the decline of the dopaminergic activity, since this activity is age-related (American Psychiatric Association, 2013). The age effect on the onset of the disorder is possibly related to gender, with male individuals presenting worse premorbid adaptation, lower academic performance, more prominent negative symptoms (NSs) and cognitive impairment, and, in general, a worse prognosis (American Psychiatric Association, 2013).

Psychosis (plethora of abnormalities) is a symptom whereas, as mentioned above, SCZ is a chronic, lifelong illness, characterized by the presence of severe psychotic symptoms (American Psychiatric Association, 2013; Tandon et al., 2013). These psychotic symptoms occur over a spectrum from acute to chronic and from mild to severe and the manifestations of psychosis can be divided into positive symptoms (PSs) and NSs, both more detailed below (American Psychiatric Association, 2013). PSs are characterized by hallucinations, delusions, disorganized thinking/speech/behaviour, and disorganized or abnormal motor behaviour (American Psychiatric Association, 2013), these PSs might extend to schizotypic and dissociative states, e.g. depersonalization, found outside of SCZ itself (O'Connor & Lecomte, 2011). Whereas NSs are characterized by diminished emotional expression, avolition, alogia, anhedonia, and asociality (American Psychiatric Association, 2013). The psychotic symptoms of SCZ are relatively severe and quite specific for this disorder (Heinz et al., 2016; Soares-Weiser et al., 2015) and they include PSs like hallucinations and delusional perceptions, experiences of thought interference, and passivity experiences (Cutting, 2015; Soares-Weiser et al., 2015).

The hallucination is an experience similar to a perception that has the clarity and impact of a true perception but occurs without an external stimulation from a relevant sensory organ. Hallucinations can be divided in auditory (involves the perception of sounds, the most common is hearing voices), congruent with mood, geometric (visual hallucinations involving geometric shapes such as tunnels and funnels, spirals, trellises or spider webs), gustatory (involves the perception of taste, it is usually unpleasant), incongruent with mood, olfactory (hallucination involving the perception of odour, such as burning rubber or decaying fish), somatic (involves the perception of physical experience located within the body, e.g., a sensation of electricity), tactile (involves the perception of touch or the presence of something under the skin, the most common is the sensation of electric shocks and toggling, there is also the sensation of something crawling over or under the skin), and visual (involves the vision, which can consist of images with shape, such as people, or images without form, such as flashes of light) (American Psychiatric Association, 2013).

Delusions are false beliefs based on an incorrect inference about external reality that is firmly held despite what the majority of people believe and despite incontestable and obvious evidence to the contrary, and they can be divided into bizarre (involves a phenomenon that a person's culture would consider physically impossible), delusional jealousy (delusion that the sexual partner is unfaithful), congruent with mood, of reference (delusion in which facts, objects or other people around are perceived as having a particular and unusual meaning, these are usually negative or pejorative in content, but they can also be grandiose), of being controlled (feelings, impulses, thoughts or actions are experienced as being under control of some external force rather than under the control of the individual himself), erotomaniac (delusion that another person, usually of a higher position, is in love with them), grandiose (delusion of inflated worth, power, knowledge, or identity or of having a special relationship with a deity or famous person), incongruent with mood, thought insertion (delusion that certain thoughts are not theirs but are inserted in their mind), thought broadcast (delusion that one's thoughts are being broadcast aloud so that they can be perceived by others), persecutory (delusion in which the central theme is that the individual, or someone close to him, is being attacked, persecuted, cheated, harassed or the victim of a conspiracy), somatic (delirium whose main content concerns appearance or functioning of the body itself), and finally can be of mixed type (American Psychiatric Association, 2013).

To diagnose SCZ, 2 diagnostic systems were implemented: the Diagnostic and Statistical Manual of Mental Disorders (DSM) in the 50s (https://courses.lumenlearning.com/abnormalpsychology/chapter/history-of-the-dsm), and the International Classification of Diseases (ICD) in 1900 (Hirsch et al., 2016). Nowadays the diagnostic systems used are the 5th edition of DSM (DSM-5) and the 10th revision of ICD (ICD-10). The diagnostic criteria of DSM-5 and ICD-10 were made to achieve 3 different goals: to identify groups of patients with broadly similar clinical presentation and prognosis, to facilitate early diagnosis and choice of treatment, and finally to define a homogenous heritable diagnostic category for genetic and other aetiological research (Kendell & Jablensky, 2003).

1.2.1 DSM-5

The DSM is a manual detailing diagnostic criteria for mental health disorders and substance use disorders (Center for Behavioral Health Statistics and Quality, 2016), and was issued by the American Psychological Association having its 1st edition published in 1952, the 2nd edition in 1968, the 3rd edition in 1980, the 4th edition in 1994, and finally the

5th edition, which has been the official diagnostic system since 2013 (https://courses.lumenlearning.com/abnormalpsychology/chapter/history-of-the-dsm/).

According to the American Psychiatric Association (2013), the psychotic disorder is considered to last for more than a day and less than a month. The schizophreniform disorder is characterized by a symptomatic presentation equivalent to SCZ, except for the duration (less than 6 months) and the absence of the requirement for functional decline. On the other hand, to be diagnosed with SCZ, the patient needs to have 2 or more symptoms from delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behaviour, and NSs (diminished emotional expression or apathy), for 1 month (less if treated), and at least one of those symptoms should be delusions, hallucinations, or disorganized speech. The patient needs to present continuous signs of disturbance, persistent for at least 6 months, and this period must include at least 1 month of the symptoms mentioned above (or less if treated), and can include periods of prodromal or residual symptoms [they can be characterized by mild forms or at subclinical levels of hallucinations or delusions (American Psychiatric Association, 2013)]. During these prodromal or residual periods [time interval between the onset of the 1st prodromal symptom and the onset of the characteristics signs/symptoms of the fully developed illness (Molnar, Feeney, & Fava, 1988)], the signs of the disturbance may be manifested only by NSs or by 2 or more symptoms present in an attenuated form. The specifications should only be used after 1 year of follow-up if they are not in contradiction with the diagnostic course criteria. The characteristic symptoms of SCZ involve a range of cognitive, behavioural, and emotional disorders, but none of the symptoms are pathognomonic of the disorder (American Psychiatric Association, 2013). Substance-induced psychotic disorders [condition caused by the use of or withdrawal from drugs (Casarella, 2020)] are placed in the category of 'Schizophrenia Spectrum and Other Psychotic Disorders'. The diagnosis of Cannabis-Induced Psychotic Disorder (CIPD) is given when hallucinations or/and delusions are present; these develop during or soon after Cannabis intoxication. The disturbance that Cannabis produces should be seen and cannot be better explained by an independent psychotic disorder that is not Cannabis-induced and only psychotic symptoms occurring in the recent intoxication are thought to lead to CIPD diagnosis (American Psychiatric Association, 2013).

The difference between a Cannabis Intoxication (a DSM diagnosis) and CIPD is that in CIPD the hallucinations and/or delusions are the focus of the clinical presentation and are severe enough to warrant clinical treatment/attention. While in Cannabis Intoxications the psychotic symptoms are mild and self-limited and are not required to make the diagnosis. The hallucinations in CIPD are experienced without insight, while in the Cannabis Intoxications they are experienced with insight intact, and they are

considered by DSM-5 to be perceptual disturbances. The high intensity/severity of the symptoms of CIPD also have a much longer duration, from days to even weeks, although it can also last for some hours if the symptoms are severe. In Cannabis Intoxication it is resolved within 24 hours (D'Souza et al., 2016; Pearson & Berry, 2019).

1.2.2 ICD-10

The 1st edition of the International Statistical Classification of Diseases and Related Health Problems or more commonly known as ICD, was published with a different name for the 1st time in 1900, the 2nd revision in 1910, the 3rd revision in 1920, the 4th revision in 1929, the 5th revision in 1938, and in 1948 the World Health Organization took charge of this classification system, renamed with the present name and in the same year published the 6th revision (Hirsch et al., 2016). The 10th revision (ICD-10), endorsed in May of 1990, is used as the official diagnostic system instead of the DSM by more than 150 countries (World Health Organization, 2021). Although the ICD-10 is currently the official revision, some studies used the ICD-8 (published in 1968), and ICD-9 (published in 1977) (Hirsch et al., 2016) posteriorly to ICD-10 (Allebeck, Adamsson, Engstrom, & Rydberg, 1993; Andreasson, Allebeck, Engstrom, & Rydberg, 1987; Andreasson, Allebeck, & Rydberg, 1989; Hambrecht & Hafner, 2000; Manrique-Garcia et al., 2012; Nielsen, Toftdahl, Nordentoft, & Hjorthoj, 2017; Zammit, Allebeck, Andreasson, Lundberg, & Lewis, 2002). From January 1st, 2022, the 11th will be officially released (World Health Organization, 2021).

The ICD-10-based diagnostic of SCZ requires at least 1 of the following criteria to diagnose a patient with SCZ: echo, insertion or withdrawal, broadcasting; delusional perception and delusions of control, influence, or passivity; hallucinatory voices commenting or discussing with the patient in the 3rd person; and persistent delusions that are culturally inappropriate and completely impossible. Or at least 2 of the following: persistent hallucinations in any modality, when accompanied by delusions; neologisms, breaks or interpolations in the train of thought and incoherence; catatonic behaviour; and NSs, such as apathy, paucity of speech, emotional blunting, or incongruity. Its course can be either continuous, or episodic with a progressive or stable deficit, or there can be one or more episodes with complete or incomplete remission. Furthermore, it should be present most of the time during an episode of psychotic illness lasting for at least 1 month, whereas the period of observation is at least 1 year. The SCZ diagnosis should not be made in presence of extensive depressive or manic symptoms, except if the schizophrenic symptoms precede the affective disturbance, or in the presence of brain

disease or during states of drug intoxication or withdrawal (Kendell & Jablensky, 2003; World Health Organization, 1992).

For the diagnosis of schizophreniform or, as in ICD-10, of acute schizophrenia-like psychotic disorder, the psychotic symptoms should be comparatively stable, but they last for less than a month and the polymorphic unstable features need to be absent. If the psychotic symptoms persist even after one month, then the diagnosis needs to be changed to SCZ (World Health Organization, 1992)

A psychotic disorder in a mental and behavioural syndrome due to psychoactive substance use is a group of psychotic phenomena that occurs or follows the use of psychoactive substance but that are not explained based on acute intoxication alone and are not in a withdrawal state. It is characterized by hallucinations (majority auditory, but usually in more than one sensory modality), perceptual distortions, delusions (majority paranoid or of persecutory nature), psychomotor disturbances (excitement or stupor), and an abnormal affect (World Health Organization, 1992).

1.2.3 Comparison of diagnostic systems

There are some similarities between these two systems. For instance, both require the presence of an active phase of the symptoms through at least 1 month. The criteria for both systems refer to characteristic symptoms present in the cross-section of the clinical picture, weighted differently for diagnostic significance, the duration of symptoms required for a reliable ascertainment, and finally the longitudinal pattern (Jablensky, 2010).

There are some differences between the ICD-10 and the DSM-5 in terms of diagnosing SCZ. The ICD-10 was designed as a family of inter-related versions addressing different users, while the DSM-5 provides a single set of operational diagnostic criteria for all users. The ICD-10 defines SCZ as a group of disorders, while the DSM-5 suggests a unitary view of the disorder. The requirement of having 6 months with any disturbance, which include the prodromal and residual symptoms, that relegates the cases of shorter duration to the schizophreniform disorder, is absent in the ICD-10, since only 4 weeks is needed to eliminate the majority of acute non-schizophrenic psychoses that are associated with the use of substances. The DSM-5 also requires the presence of social or occupational dysfunction as part of the definition of SCZ, while the ICD-10 is context-dependent and not an invariant attribute of the clinical syndrome (Jablensky, 2010).

1.3 Cannabinoid-induced schizophrenia

It is a fact that environmental exposure may cause psychiatric symptoms or disorders and that such effects may be more present among individuals that are already predisposed to the psychiatric disorder, and to this day there are studies and convincing evidence that premorbid use of Cannabis is likely a one of many risk factors of the schizophrenia spectrum disorder (SSD) (Ramsay & Compton, 2011). Some studies found that Cannabis consumption during a critical period of brain development could serve as a contributor of later psychiatric illness through effects on important neurobiological systems, which is coherent with both the largely accepted neurodevelopment theory and diathesis-stress model of SCZ (Ashtari et al., 2009; Realini, Rubino, & Parolaro, 2009).

Cannabis-induced psychosis (CIP) is a psychosis that happens after the administration of Cannabis. Depending on the way of administrations and the individuals, the symptoms can appear immediately after, after several hours, or even after days. Contrarily, SCZ can only be diagnosed if there are no substances involved in the symptoms of the individual. But many investigators have argued that CIP might be an early sign of SCZ rather than a distinct clinical entity (Arendt, Mortensen, Rosenberg, Pedersen, & Waltoft, 2008). Arendt, Rosenberg, Foldager, Perto, and Munk-Jorgensen (2005) found that 50% of the patients with CIP received an SSD diagnosis within a mean period of follow up of 5.9 years. The study of Crebbin, Mitford, Paxton, and Turkington (2009) found that in 35 first-episode psychosis (FEP) cases [FEP is when there is the presence of delusions, hallucinations, thought disorder, bizarre or distorted behaviour, NSs, mania, or clinical suspicion of psychosis and no previous contact with psychiatric services for the psychotic symptoms were yet placed (Kokona et al., 2017)], diagnosed with drug-induced psychosis, one third developed an SSD within 2 years. In a study by Caton et al. (2007) one fourth of the patients in the early-phase psychosis diagnosed with substance-induced psychosis received a primary psychotic disorder diagnosis after 1 year. Some studies found that the use of Cannabis is associated with a 2-fold higher risk of developing psychosis (Henquet, Murray, Linszen, & van Os, 2005; Moore et al., 2007). Others found that the use of Cannabis generally precedes the development of these disorders, and provokes an early onset of SCZ. For example, Donoghue et al. (2014) found that Cannabis users developed SCZ 2.7 years earlier than non-users. If considering the daily use of high-potency Cannabis, it would increase this difference to 6 years (Di Forti et al., 2014). Stefanis et al. (2013) suggested that the early age of onset of psychotic disorders among users of Cannabis is not associated with the age *per se*, but with the period of use.

In a study by Kristensen and Cadenhead (2007), which involved 48 individuals at ultra-high risk, it was found that at 1-year follow-up, only 1 out of 32 subjects that had Cannabis or minimal use of Cannabis had converted to psychosis (3.1%), while 5/16 (31.3%) met the criteria for Cannabis abuse or dependence. The use of Cannabis appears as a risk factor for the development of SCZ-like psychotic disorders (Henquet, Murray, et al., 2005; Moore et al., 2007), but among regular users, only 3% develop psychosis (Murray, Morrison, Henquet, & Di Forti, 2007).

To answer the many existing questions about this association, many hypotheses have been proposed. One systematic review (Smit, Bolier, & Cuijpers, 2004) analysed 5 population-based, longitudinal studies (Arseneault et al., 2002; Fergusson, Horwood, & Swain-Campbell, 2003; van Os et al., 2002; Weiser, Knobler, Noy, & Kaplan, 2002; Zammit et al., 2002) to address 5 hypotheses about this association. Two of them, regarding self-medication hypothesis and co-occurring drug use, were eliminated. The hypothesis of the cofounding effects needed more research to be ruled out potential. The last 2 hypotheses, one on the potential of Cannabis use to increase the risk of SCZ development, especially in vulnerable individuals, and on Cannabis unique contribution to the increased risk for SCZ, were considered viable.

There is also the hypothesis of “window of vulnerability”, which postulates that the period of development and maturation is critical in the early adolescence where the brain is very susceptible to the psychotic effects of Cannabis (Radhakrishnan, Wilkinson, & D'Souza, 2014). This is a phase where many processes take place, such as neuronal migration and differentiation, synaptogenesis, axon formation, and dendritic proliferation, myelination, pruning, apoptosis, and the activity-dependent changes [these changes begin in the uterus and continuous to early 20s or later (Molina-Holgado et al., 2002)], and the use of Cannabis might disrupt these processes (Vindenes & Mørland, 2017).

Many studies support the hypothesis found in the study of D’Souza, et al. 2004, which distinguishes between the exogenous hypothesis, where the cannabinoids like Δ^9-THC produce psychotic disorders by mechanisms extrinsic to the pathophysiology of naturally occurring psychoses, and the endogenous hypothesis, where the components of the ECS, like CB1, are dysfunctional, which contributes to the pathophysiology of SCZ (or some of its subtypes), perhaps unrelated to the cannabinoid ingestion.

Susser (1991) used the Hill (1965) criteria, which is strength, consistency, specificity, biological gradient, temporality, coherence, and plausibility, to distil 3 properties that may define the causes for Cannabis potentially causing SCZ, as well as an exposition of 3 main criteria for establishing causality, which is the association, the cause and the disease appearing together. The temporal priority, the putative cause is present

before the disease, and the direction, changes in the putative cause lead to changes in the outcome, as opposed to being driven by a confounding 3rd variable.

The stronger an association, the more likely is to have a casual component (Ramsay & Compton, 2011). So, the use of Cannabis has a weak but consistent association with psychotic disorders. In the review (of 7 prospective studies) of Henquet, Murray, et al. (2005) it was found that the effect persisted after the analysis was controlled for various potential confounding factors. Although this association is relatively weak compared to other casual risk factors for SCZ, some established environmental risk factors for SCZ, like obstetric complications during birth and a history of sexual abuse, have a similar effect size (OR: 2.0, CI: 1.6-2.4 and OR: 2.9, CI: 1.3-6.4, respectively) (Bebbington et al., 2004; Clarke, Harley, & Cannon, 2006). As it was mentioned above, the relationship between Cannabis use and psychotic disorders are consistent (Ramsay & Compton, 2011), but not only it is associated with SCZ, more broadly defined psychotic disorders, and psychotic symptoms, but Cannabis use has also been associated with greater schizotypy, which is a personality characterized by anhedonia, ambivalence, interpersonal aversiveness, body image distortion, cognitive slippage, and sensory, kinesthetics, or vestibular aberrations (Meehl, 1962; Rado, 1960), among undergraduate college students (Bailey & Swallow, 2004; Dumas et al., 2002; Nunn, Rizza, & Peters, 2001; Schiffman, Nakamura, Earleywine, & LaBrie, 2005), as well as symptoms consistent with the prodrome (early or premonitory sign or symptoms of a disorder (American Psychiatric Association, 2013)) among adolescents (Miettunen et al., 2008).

In terms of specificity, where the factor influences specifically a particular outcome or population (Ramsay & Compton, 2011), L. Arseneault, M. Cannon, J. Witton, and R. Murray (2004a) and L. Arseneault, M. Cannon, J. Witton, and R. M. Murray (2004b) observed that many studies indicate both specificity of the exposure (the use of Cannabis) and specificities of the outcome (SCZ and other psychosis-related outcomes) (Arseneault et al., 2002; van Os et al., 2002; Zammit et al., 2002).

In the majority of studies that studied the temporal sequence of Cannabis use and psychosis, it was found that the first-episode patients reported initiating the use of Cannabis before the onset of psychotic symptoms, in some cases by several years (Bersani, Orlandi, Gherardelli, & Pancheri, 2002; Compton & Ramsay, 2009). And some studies found that many individuals with a recent-onset psychosis stated that they initiated the use before the first sign of the prodrome (Compton et al., 2009; Compton & Ramsay, 2009).

When it comes to the biological gradient, which is when the outcome increases monotonically with the increase of dose exposure or according to a function predicted by a substantive theory, larger doses, or longer exposure to Cannabis (particularly in early

adolescence) appears to be related with a higher risk for psychosis and an accelerated onset of psychosis (Ramsay & Compton, 2011). Many studies compare patients in dichotomized groups. They can be with the presence or absence of the use of Cannabis beyond a certain threshold or with the presence or absence of a Cannabis use disorder (Ramsay & Compton, 2011). Henquet, Krabbendam, et al. (2005) showed a dose-response relationship between the use of Cannabis and psychotic outcomes, with odds ratio (OR) of developing psychosis gradually increasing with the frequency of use, ranging from 1.0 (CI: 0.5-1-9) among those using Cannabis once a month or less, to 2.6 (CI: 1.5-4.3) among daily users.

The biological plausibility is the observed association that can be reasonably explained by substantive explanations (Ramsay & Compton, 2011). And there are several possible mechanisms by which Δ^9-THC might increase or cause positive, negative, and cognitive symptoms of SCZ (D'Souza et al., 2005; D'Souza, Perry, et al., 2004). For instance, the effect of cannabinoids on increasing mesolimbic dopaminergic activity might explain the fact that PSs can be induced by Δ^9-THC (D'Souza, Cho, Perry, & Krystal, 2004).

Regarding the specific phenotypes (or endophenotypes), the administration of Δ^9-THC in healthy volunteers results in an impairment in visual information processing that is similar to those observed in individuals with SCZ or those who are at a high risk of developing the disorder (Koethe et al., 2006). Many researchers are studying several aspects of EC ligands, such as the CB1, and genetic polymorphisms that could further elucidate the biological plausibility of the association between Cannabis and psychosis (Ramsay & Compton, 2011). The randomized experiments are very important since the causation is more likely if the evidence is based on these types of experiments and the experimental administration of Δ^9-THC is going to support the notion that this agent is going to induce various experiences like those observed in SCZ, that the observational one could not do (Ramsay & Compton, 2011). The ECS is involved in many important functions that are relevant to SCZ (Wobrock et al., 2011). For instance, CB1 is abundantly expressed at the presynaptic terminals in regions involved in cognition, specifically in learning and memory, in the hippocampus, the prefrontal cortex, the anterior cingulate, the basal ganglia, and the cerebellum (Wilson & Nicoll, 2002). The ECS (through anandamide and 2-AG) mediates the flow of information in the brain through retrograde signalling, modulating inhibitory and excitatory neurotransmitter release crucial for synaptic plasticity, depolarization-induced suppression of inhibition or excitation, long-term potentiation (and therefore learning), memory and other cognitive functions (Piomelli et al., 2000). So, this system interacts through the CB1 with various other neurotransmitter systems, including

the glutaminergic and dopaminergic systems, that have been implicated in the aetiology of SCZ (Piomelli et al., 2000).

Although substantial findings strengthen the theory that Cannabis might have a causal effect in SCZ, not every study validates this concept. Other plausible theories have been proposed to explain this link (Ramsay & Compton, 2011). For example, Degenhardt, Hall, and Lynskey (2001) found that the incidence of SCZ and the age at onset did not change with trends in the use of Cannabis, as what should be expected by using mathematical models.

Some data appears to fit well with the hypothesis that the use of Cannabis accelerates the onset of individuals with pre-existing vulnerabilities or is associated with psychosis either through reverse causality or shared diathesis (Ramsay & Compton, 2011).

About the reverse causality, it was proposed by Bersani et al. (2002) that Cannabis consumption might represent an effort to self-medicate in some to reduce NSs, rather than PSs. On the other hand, Henquet, Murray, et al. (2005) argues on this explanation for the association between Cannabis and psychosis, since many prospective studies found Cannabis being associated with later development of psychosis, even when excluding those individuals with early indicators of vulnerability. Another explanation is based on a shared diathesis between Cannabis and psychosis, since in the cohort study of Ferdinand et al. (2005) it was found that the use of Cannabis in youth predicted future psychotic symptoms, and psychotic symptoms in those who had never used Cannabis predicted future Cannabis use. So, some findings suggest a bidirectional effect, which might be supported by a shared genetic diathesis for the use of Cannabis and psychosis (Ramsay & Compton, 2011).

The seeming casual effect suggested by the replicated association could have 3 different directionalities: Cannabis use might cause psychosis; or in those individuals with underlying vulnerabilities, psychosis may make individuals more likely to consume Cannabis; and finally there is a shared diathesis that may underlie both outcomes (Ramsay & Compton, 2011). The first theory is viewed as the most probable explanation and is explored further below through a consideration of criteria for establishing causality.

There are many studies about this association at different levels, from epidemiological studies (Allebeck et al., 1993; Andreasson et al., 1987; Andreasson et al., 1989; Arseneault et al., 2002; van Os et al., 2002; Weiser et al., 2002; Zammit et al., 2002), age of onset (Dekker et al., 2012; Donoghue et al., 2014; Galvez-Buccollini et al., 2012; Sevy et al., 2010), brain physiology (Bhattacharyya et al., 2009; Delisi et al., 2006), post-mortem (Dean, Sundram, Bradbury, Scarr, & Copolov, 2001) and even genetic

relation (Bossong et al., 2009; Bossong et al., 2019; Caspi et al., 2005; Costas et al., 2011; Lodhi et al., 2017; Zammit et al., 2007).

Several findings indicate that Cannabis plays a causal role in the onset of psychosis (Ferdinand et al., 2005), many of them are large-scale epidemiological studies that give credibility to the allegation that Cannabis use may be a component cause of SCZ. The first study to find evidence in the association between Cannabis and SCZ was the study of Andreasson et al. (1987), a Swedish national cohort involving over 50,000 Swedish conscripts, where it was observed a dose-response relationship between the use of Cannabis at conscription and the diagnosis of SCZ, demonstrating a convincing dose-relationship between the use of Cannabis and subsequent risk of SCZ. It was observed that young men (18 years old), self-reported as heavy Cannabis users, were 6 times more likely to be later diagnosed with SCZ. Although very few (3%) of heavy Cannabis users developed SCZ, it indicates that the use of Cannabis may increase the risk of developing SCZ only among individuals that are already vulnerable to develop psychosis, it supports the view that Cannabis might act as an independent risk factor for SCZ, and supports a dose-response relationship between Cannabis and SCZ diagnoses.

Zammit et al. (2002) did a follow-up study of the same cohort that showed that Cannabis users were 6.7 times more likely than non-users to be diagnosed with SCZ 27 years later, even when controlled for potential confounding variables, concluding that the observations are consistent with a causal relationship between the use of Cannabis and SCZ.

van Os et al. (2002), found, in a study of 4,000 individuals in the general population, that those using Cannabis at baseline were nearly 3 times more likely to manifest psychosis 3 years later compared to non-users, even after controlling for potential confounders; it was also observed a dose-response relationship. They concluded that the use of Cannabis is an independent risk factor for the emergence of psychosis in psychosis-free people and that those with vulnerability to psychotic disorders are particularly sensitive to its effects, resulting in a poor outcome.

Arseneault et al. (2002) observed a general population birth cohort of over 1,000 individuals. 10.3% of those using Cannabis at the ages between 15 and 18 had higher rates of being diagnosed with the schizophreniform disorder at age of 26 compared to non-users (3%), and the effect was stronger the earlier the use, concluding that the use of Cannabis in adolescence increases the likelihood of experiencing the symptoms of SCZ in adulthood.

In another birth cohort of 4,000 individuals, it was found that early initiation of Cannabis use (before age of 15 years) was linked with an increased risk of nonaffective psychosis. This association continued when assessed in sibling pairs, thus reducing the

likelihood that this relationship was driven by residual confounding due to unmeasured shared genetic and/or environmental influences (McGrath et al., 2010).

The majority of the evidence suggests that the use of Cannabis is related to greater levels of PSs, since in the study of D'Souza et al. (2005) it was found that Δ^9-THC transiently increases PSs in a sample of individuals with SCZ (Grech, Van Os, Jones, Lewis, & Murray, 2005; Van Mastrigt, Addington, & Addington, 2004; Wade et al., 2006). And in the study of Koen, Jonathan, and Niehaus (2009), the frequent use of Cannabis was related to an increase in hallucinations, delusions, thought disorders, and bizarre behaviours. Bersani et al. (2002), found that in a group of Cannabis users, the hallucinations were greater among those who started using Cannabis before the onset of SCZ and that this association was not present when comparing those who initiated after the onset of the illness.

Several studies found that individuals that consistently consumed large amounts of Cannabis have an increased risk of developing SCZ-like symptoms later in life (Kuepper et al., 2011; Moore et al., 2007; Potter, Clark, & Brown, 2008; Radhakrishnan et al., 2014). In a study where it were investigated 280 cases presenting FEP, it was found that FEP was not more likely to occur in individuals who had used Cannabis or those that started to use earlier than the control group, but psychosis was indeed associated with a more frequent and long-lasting Cannabis use (Di Forti et al., 2009). Di Forti et al. (2014) also found that individuals that smoked Cannabis with high potency every day had the earliest onset of psychosis, compared to the group of individuals that never used Cannabis, as daily users had an average onset of psychosis of 6 years before the non-users.

Many studies associate the use of Cannabis and the age of onset of psychotic symptoms (Ramsay & Compton, 2011). Some found that Cannabis users had an earlier age of onset of psychosis than non-users (Barnes, Mutsatsa, Hutton, Watt, & Joyce, 2006; Mauri et al., 2006; Van Mastrigt et al., 2004; Veen et al., 2004). Although the study of Gonzalez-Pinto et al. (2008) included patients with non-affective and affective psychoses, it was found a decrease in age at onset of psychosis of 7, 8.5, and 12 years in individuals with Cannabis use, abuse, and dependence, respectively, when compared with non-users.

Compton et al. (2009) found that there is an early progression to frequent premorbid Cannabis use associated with an early age at the onset of prodromal symptoms and psychotic symptoms. Arseneault et al. (2002) found that the earlier the use of Cannabis is initiated, the greater the risk of developing a psychotic disorder.

In contrast, the study of Bersani et al. (2002), patients with SCZ that used Cannabis did not have a significantly younger age at onset of symptoms than non-users. Although Sevy et al. (2010) found that compared to non-substance-abusing first-episode patients,

those with a Cannabis use disorder had an earlier age at onset of PSs. However, this association did not persist when controlling for many other demographic and clinical variables, like gender and premorbid adjustment.

Other studies suggested that the earlier the exposure to Cannabis, the greater the risk of a psychotic outcome (Arseneault et al., 2002; Casadio, Fernandes, Murray, & Di Forti, 2011; Di Forti et al., 2014; Sewell, Ranganathan, & D'Souza, 2009). The greater risk in those who started Cannabis use earlier can be due to the high cumulative exposure to Cannabis in early users and, adolescence is a period with an increased vulnerability to Δ^9-THC during the critical phases of brain maturation, like in early puberty (Casadio et al., 2011; Copeland, Rooke, & Swift, 2013), since during adolescence the levels of ECs and cannabinoid receptors increase, with a peak in puberty (Schneider, Schomig, & Leweke, 2008).

With all the evidence available, it was suggested that premorbid Cannabis use is a component cause of SCZ, rather than being a sufficient cause or necessary cause, which means that it probably contributes to forming a complex casual constellation, along with other component causes, that lead to the disorder (Arseneault et al., 2004a; Arseneault et al., 2004b; Di Forti & Murray, 2005). Overall, the findings suggest that the use of Cannabis doubles the risk of developing SCZ in the long term (Arseneault et al., 2002; Arseneault et al., 2004b). But as pointed out by McGrath et al. (2010), the relationship is probably not unidirectional, as individuals that are vulnerable to developing psychotic disorders might be more likely to initiate the use of Cannabis, which could consequently contribute to an increased risk of disorder.

There is a question that pertains to why only a small portion of individuals that use Cannabis develop psychotic symptoms or SCZ, but the use of Cannabis is conceptualized as a component cause rather than a sufficient cause, making its use act in conjunction with genetic susceptibilities or with other environmental risk factors (Di Forti & Murray, 2005; Ramsay & Compton, 2011). So, Caspi et al. (2005) found that a functional polymorphism in the catechol-O-methyltransferase (COMT) gene moderated the influence of the use of Cannabis in adolescents on developing adult psychosis, particularly the carriers of the valine allele are more likely to develop psychotic symptoms and to develop the schizophreniform disorder if they had used Cannabis, but the use of Cannabis did not have those adverse influences on those with 2 copies of the methionine allele. Another study (Pelayo-Teran et al., 2010) found evidence that suggests that this same gene-environment interaction might be related to the age at onset of psychosis among first-episode patients.

Arseneault et al. (2004b) reviewed 5 studies that included properly delineated samples drawn from population-based registers or cohorts and controlled for diverse

potential confounders (Andreasson et al., 1987; Arseneault et al., 2002; Fergusson et al., 2003; van Os et al., 2002; Zammit et al., 2002), and computed a pooled OR of 2.3 (95% confidence interval (CI), 1.7-2.9).

There is a SR that used 11 studies that examined the relationship between the use of Cannabis and psychosis, that found a pooled OR of 2.9 (95% CI: 2.4-3.6), which suggests that Cannabis use is an independent risk factor for psychosis and the development of psychotic symptoms in non-clinical samples (Semple, McIntosh, & Lawrie, 2005). Two years later, Moore et al. (2007), reviewed 35 studies and revealed an increased risk of any psychotic outcome in non-user individuals, with a pooled adjusted OR of 1.4 (95% CI: 1.2-1.6), and results were consistent with a dose-response effect.

There are several limitations in many studies conducted to date, that include the diversity of operationalizations of psychosis outcomes, the fact that measures of the use of Cannabis are usually based on self-report and not complemented by objective biological assays, potential confounding by the effects of other concurrently used drugs, and difficulty in ruling out the possibility that prodromal manifestations of SCZ precede Cannabis use (Arseneault et al., 2004b; Di Forti & Murray, 2005).

There is a model that is very useful and explains how and why a subject develops SCZ, and that is the “gene x environment” interaction model, which includes the genetic and environmental risk factors, that combine to influence the risk of developing SCZ and psychotic disorders (Schizophrenia Working Group of the Psychiatric Genomics, 2014; van Os, Rutten, & Poulton, 2008).

Andreasen (2000) found that using neuroimaging techniques in brain abnormalities identified in SCZ, shows evidence for structural and functional impairment in multiple brain regions with a focus on the frontal cortex, temporal cortex, thalamus, hippocampal complex, basal ganglia, and the cerebellum. It was suggested that the abnormalities of the temporal lobe structures linked to the mesolimbic system is responsible for the cognitive and emotional disturbances that are common in SCZ (Shenton et al., 1992), meanwhile, the temporal volume reductions have been linked to clinical features (Gur et al., 2000).

The reduction of the bilateral hippocampal size has been associated with memory deficits, and the decrease of the total volume of the superior temporal gyrus is related to the severity of thought disorder and auditory hallucinations (Barta, Pearlson, Powers, Richards, & Tune, 1990; Shenton et al., 1992).

There has been suggested by neuroimaging studies that Δ^9-THC might increase dopamine release in the nucleus accumbens, inhibiting, via CB1 activation, the release of glutamate on to GABAergic neurons that project from the nucleus accumbens to the ventral tegmental area. This lifts the inhibitory effect on the firing of dopaminergic neurons which project back to the nucleus accumbens (Pertwee, 2008). Such a model explains

how Δ^9-THC can affect dopamine levels in cerebral regions, including the striatum, which is implicated in the pathogenesis of psychotic symptoms and offers crucial information to understand the biology of CIP (Morrison & Murray, 2009). It also seems like Δ^9-THC can exert opposite effects, such as stimulating or inhibiting the CNS transmission via the activation or blockade of the CB1 (Berrendero, Sepe, Ramos, Di Marzo, & Fernandez-Ruiz, 1999). This model also fits with the findings that genetic variation at the AKT1 gene (a gene that influences post-dopamine 2 receptor signalling) renders some individuals more vulnerable to CIP (Di Forti et al., 2012; van Winkel, van Beveren, Simons, & Genetic Risk and Outcome of Psychosis (GROUP) Investigators, 2011). Englund et al. (2013) showed that by pre-treating healthy subjects with CBD, it reduces the Δ^9-THC induced paranoia, and also inhibits the detrimental effects of the Δ^9-THC on episodic memory. This can explain why the high potency Cannabis, which has high levels of Δ^9-THC and almost no CBD, is related to the highest risk of psychosis (Di Forti et al., 2015; Di Forti et al., 2009).

There are specific genetic factors that may moderate the effects of the exposure of Cannabis on the risk for psychosis, the majority of available studies to date focus on the COMT gene, the neuregulin 1 gene, and the CB1 gene (D'Souza, Sewell, & Ranganathan, 2009). The most noteworthy genetic interaction effect on Cannabis abuse and psychosis goes to the COMT polymorphism (Wobrock et al., 2011). COMT is an enzyme that is involved in the breakdown of dopamine in the synapse, and the functional polymorphism (Val108/155Met) of the COMT gene results in the 2 allelic variants influencing the efficacy of dopamine metabolism, especially in the prefrontal cortex (Meyer-Lindenberg et al., 2006). The valine allele leads to higher expression of COMT and lower levels of dopamine in the prefrontal cortex, and the following increase in the dopamine levels in the midbrain neurons that projects to the ventral striatum (Meyer-Lindenberg et al., 2006).

In the study of Henquet et al. (2006), it was found that carriers of the Val allele were more sensitive to Δ^9-THC induced psychotomimetic effects than Met carriers, but only if they had prior evidence of psychometric psychosis liability. In another birth cohort study, it was found that carrying the COMT valine allele leads to a 5-fold higher risk to suffer from psychotic symptoms, and a 2-fold increase in the risk for SCZ in adults if they used Cannabis frequently in adolescence (Adler et al., 1982).

The best predictions for the association between Cannabis use and psychotic symptoms can be, in summary, early age for initiating Cannabis use, frequent use, the high potency Cannabis (Di Forti et al., 2015; Di Forti et al., 2009), and genetic vulnerability (Caspi et al., 2005; Di Forti et al., 2014; Henquet, Murray, et al., 2005; van Winkel et al., 2011).

2 Aims

The present Dissertation aimed at collecting available scientific publications regarding the association of cannabinoids abuse and the incidence of SCZ, in the form of a systematic review.

A comprehensive discussion of several types of human studies, from epidemiological to genetic findings, was conducted to evaluate the plausibility and causality of Cannabis use as a trigger of SCZ.

3 Methods

There are many types of studies, and they can be separated into primary and secondary studies. Primary studies can be subdivided into observational and experimental ones. The secondary studies comprise meta-analysis and systematic reviews. Both use the existing scientific literature on empirical data, compiling the most robust evidence into one theoretical study (Rodrigues, 2012). Meta-analysis as defined by Huque (1988) is ‘A statistical analysis that combines or integrates the results of several independent clinical trials considered by the analyst to be ‘combinable.’’, although this definition is still debatable. Meta-analysis portrays the statistical integration of separate studies (Egger & Smith, 1997), or a ‘statistical analysis of a large collection of analysis results from individual studies for the purpose of integrating the findings’ (Glass, 1976).

On the other hand, the systematic review is described as a way to denote any review of the body of data that uses well-defined methods and inclusion/exclusion criteria, which may include a meta-analysis, appraisals of single trials, and other sources of empirical evidence (Egger & Smith, 1997).

This systematic review was based on the work of Donato and Donato (2019), which determines the essential steps of the process of organizing a systematic review. The flow diagram presented on Figure 7 was designed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, depicting the flow of data through the different phases, and maping out the number of identified records, included publications, and the applied exclusion criteria. As shown in Figure 7, the search engines used were PubMed, Scielo, Science.gov, BMC, Cochrane, and Google Scholar. Although the use of the latter database is controversial, it was used due to a large number of results retrieved. Some studies were obtained from other sources, including other systematic reviews and studies that could be pertinent to the

present work. For database, it was used a different combination of keywords, adapted to the search criteria of each engine. As shown in Figure 7, the keyword “Cannab*” was used, whenever allowed by the engine, so it would include every word starting with this term, such as Cannabis, cannabinoids, Δ^9-THC, CBD, cannabivarin, and many others. Each combination of keywords was carefully selected in order to obtain the maximum results of each search engine.

The exclusion criteria used for this systematic review were the following: duplicates; studies in idioms other than English, Portuguese and Spanish; conference abstracts or articles that were not fully available; animal studies; *in vitro* and *in situ* studies; studies comprising symptoms of SCZ other than PSs or psychosis; letters to the Editor; comments; reviews; meta-analysis; systematic reviews; research notes; studies on the treatment of SCZ or Cannabis-related complications; studies on SCZ remission; studies were Cannabis was not the main drug; *postmortem* studies; questionnaires; and studies focused on CIP but with no reference to SCZ diagnostics.

A final total of 58 studies were included in this systematic review, which fully complied with the following inclusion criteria: human studies where the association of Cannabis use with SCZ was evaluated; studies on PSs and psychosis leading to a final the diagnosis of SCZ; papers in English, Portuguese, or Spanish. Unfortunately, due to a great amount of missing data, we were unable to complement our revision work with a meta-analysis.

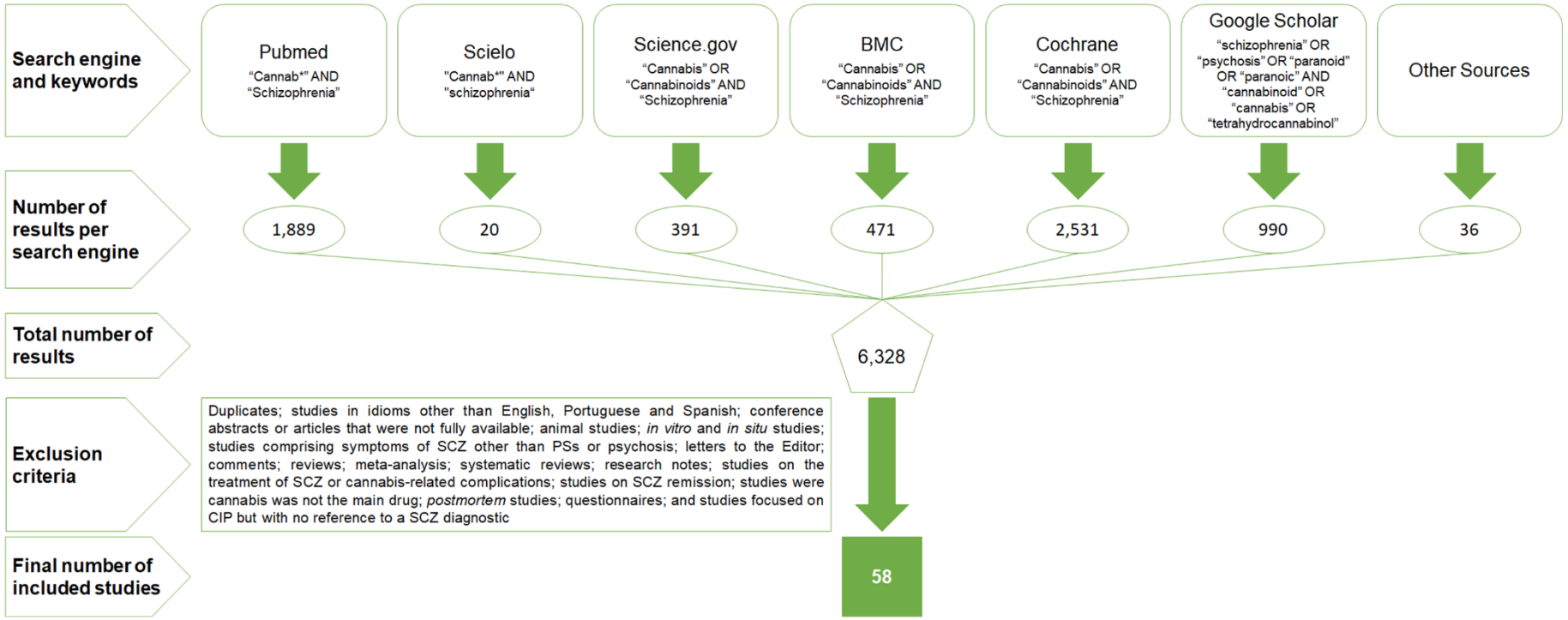

Figure 7 *Flux Diagram on the search engines, repective key-words, exclusion criteria, and total number of studies included in this systematic review. SCZ; PSs; CIP.*

4 Results

The main characteristics of the 58 studies included in this systematic review are presented in Table 2.

4.1 Epidemiological studies

Andreasson et al. (1987) aimed at evaluating the role of Cannabis as a causal factor for SCZ in the Swedish population, taking into account other factors that could act as confounders. They found a strong association between the level of Cannabis exposure and the development of SCZ. The risk of developing SCZ in the group of Cannabis users that used at least once compared to non-users was of 2.4-fold higher (95% CI: 1.8-3.3), while on those who used more than 50 times, the relative risk was 6.0 times higher (95% CI: 4.0-8.9). Two years later Andreasson et al. (1989) analysed the possible role of other drugs in causing SCZ, if Cannabis abuse preceded mental symptoms or vice-versa and what is the mode of onset and clinical course of SCZ in Cannabis abusers compared to controls, evaluating only participants from the Stockholm County. As in the previous study (Andreasson et al., 1987), they found a strong association between the level of Cannabis consumption and the treatment of SCZ. It was reported a relative risk of ddeveloping SCZ of 2.1 (95% CI: 1.1-3.8) in a group that used Cannabis at least once compared to non-users, and for those who used more than 50 times it was 4.1 (95% CI: 1.8-9.3). Both studies support the view that Cannabis has a precipitating role in the development of SCZ, with an increasing potential dependent on the level of exposure.

Allebeck et al. (1993) attempted to analyse all cases of SCZ and other psychoses in the Stockholm County, assessing the clinical features of the psychotic outcomes identified and the temporal relation between the use of Cannabis and the first symptoms of psychosis. They found that from 229 cases that had a diagnosis of Cannabis dependence and psychosis, 112 of these were diagnosed with SCZ, and 69% of the cases had a record of heavy Cannabis abuse for at least 1 year before the onset of psychotic symptoms. Supporting the hypothesis that Cannabis is a risk factor for SCZ, they also found that Cannabis-associated SCZ often has a sudden and prominent PSs. Unfortunely the authors were not able to assess the risk of SCZ among Cannabis users compared with non-users.

Table 2 - *Characteristics of the studies included in the systematic review.*

Study	Country	Number of participants	Age of the participants	Participants	Gender (% or *n*)	Follow-up period	Diagnostic system	Assessment tool
Aas et al. (2018)	Norway	1,016	18-65 years	Patients with SSD (SCZ, schizophreniform disorder, schizoaffective disorder and other psychosis), with Bipolar disorder with or without history of psychosis (bipolar I, bipolar II, bipolar not otherwise specified) and healthy controls.	Male (49.1%) and Female (50.9%)	N.R.	DSM-4	SCID-I and Affymetrix Genome-Wide Human SNP Array 6.0.
Addington and Addington (2007)	Canada	203	Mean= 25 years	Subjects that were admitted to the Calgary Early Psychosis Program.	Male (142) and Female (61)	3 years	DSM-4	SCID-I, PANSS, CDSS, Quality of Life Scale, PAS and Case Manager Rating Scale for Substance Use Disorder.
Allebeck et al. (1993)	Sweden	229	N.R.	Inpatients in the Stockholm CARE inpatients CARE register.	Male (192) and Female (37)	12 years	ICD-8 & DSM-3-R	RDC.
Andreasson et al. (1987)	Sweden	45,570	18-20 years	Swedish men conscripted for compulsory military service.	Male	15 years	ICD-8, & DSM-3	Structured Interview, Psychological Tests and 2 Non-anonymous Questionnaires.
Andreasson et al. (1989)	Sweden (Stockholm County)	7,695	18-20 years	Sub-population of Swedish males conscripted for compulsory military service from Stockholm County.	Male	15 years	ICD-8	Structured Interview and 2 Non-anonymous Questionnaires.
Arendt et al. (2005)	Denmark	535 patients 2,721 controls	N.R.	Patients treated at a Danish psychiatric hospital with a diagnosis of CIPD.	Male (441/1560) and Female (94/1161)	> 3 years, with a Mean= 5.9 years	ICD-10	DPCR and Danish Cause of Death Registry.

Table 2 - *Characteristics of the studies included in the systematic review (continued).*

Study	Country	Number of participants	Age of the participants	Participants	Gender (% or *n*)	Follow-up period	Diagnostic system	Assessment tool
Arendt et al. (2008)	Denmark	7,085	15-50 years	Data from the Danish Civil Registration System about history of psychiatric treatment in a first-degree family member and patients treatment to psychotic symptoms.	N.R.	11 years	ICD-10	DCRS and DPCR.
Barrigon et al. (2010)	Spain	112	18-57 years	Patients in their first episode of non-affective psychosis.	Male (66) and Female (46)	6 months	DSM-4	SCID-I and CIDI.
Bossong et al. (2015)	The Netherlands	17	20-44 years	Healthy volunteers with previous experience of Cannabis use without significant adverse effects.	Male (13) and Female (4)	> 2 weeks	N.R.	Positron Remission Tomography.
Boydell et al. (2007)	United Kingdom	757	> 16 years	Cases of SCZ from the Camberwell Case Register between 1965-2004.	Male (147) and Female (35)	N.R.	OCCPI	RDC
Buadze, Stohler, Schulze, Schaub, and Liebrenz (2010)	Switzerland	10	26-53 years	Patients fulfilling criteria for SCZ and for a current harmful use of/dependence from Cannabis.	Male (8) and Female (2)	1.5 hours	ICD-10	Single, unstructured, in depth interviews that were later transcripted.
Costas et al. (2011)	Spain (Valencia & Santiago de Compostela)	155	Mean= 34.2 & 37.9 years	SCZ Patients from Santiago de Compostela and SCZ patients from Valencia.	Male and Female	N.R.	DSM-4	Medical Records and Genotyping.
De Hert et al. (2011)	Belgium	766	16-65 years	Patients recruited through the outpaient and inpatient units at the University Psychiatric Centre.	Male (472) and Female (294)	3 years	DSM-4	CIDI, CGI and GAF.

Table 2- *Characteristics of the studies included in the systematic review (continued).*

Study	Country	Number of participants	Age of the participants	Participants	Gender (% or *n*)	Follow-up period	Diagnostic system	Assessment tool
Degenhardt, Hall, and Lynskey (2003)	Australia	8 birth cohorts of men and women born in 1940–44 to 1975–79	15-60 years	Patients born between 1940 and 1979.	Male and Female	30 years	N.R.	N.R.
Dekker et al. (2010)	The Netherlands	36	16-28 years	Male patients with SCZ from the open-ward inpatient and day-care units of the Adolescent Clinic of the Academic Medical Centre.	Male	N.R.	DSM-4	CGI-Severity of Illness and GAF.
Donoghue et al. (2014)	United Kingdom	143	18-64 years (<45 years)	Potential cases from the Aetiology and Ethnicity of Schizophrenia and Other Psychoses study, individuals with SCZ or schizoaffective disorder.	Male (87) and Female (56)	N.R.	ICD-10	Personal and Psychiatric History Schedule, SCAN or Item Group Checklist, Clinical Case Notes and Interviews.
Ermis et al. (2015)	Turkey	74	18-65 years	Patients diagnosed with SCZ and between ages of 18 and 65, some had a premorbid Cannabis use and others didn't.	Male	N.R.	DSM-4-TR	PANSS, Interview and Genotyping.
Estrada et al. (2011)	Spain	157	Mean= 17.01 years	Cannabis use profiles and COMT Val158Met genotypes from young Caucasian psychiatric inpatients with SSD or with non-psychotic disorders.	Male (83) and Female (74)	N.R.	DSM-4-TR	Semi-structured Interview based on the DIGS and DSM-4-TR.

Table 2 - *Characteristics of the studies included in the systematic review (continued).*

Study	Country	Number of participants	Age of the participants	Participants	Gender (% or *n*)	Follow-up period	Diagnostic system	Assessment tool
French et al. (2015)	Canada & England	1,577	12-21 years	Adolescents recruited in the context of the Saguenay Youth Study. The first replication sample consisted of 504 male youth recruited from the Avon Longitudinal Study of Parents and Children. The second replication sample consisted of 426 adolescents recruited in 8 European cities.	Male and Female	N.R.	N.R.	MRI and IMAGEN
Frisher, Crome, Martino, and Croft (2009)	United Kingdom	600,000 patients/each study year	16-44 years	Patients from the General Practice Research Database.	N.R.	10 years	ICD	General Practice Research Database, Oxford Medical Information Systems Codes, Read Codes and Office of Population and Census Statistics.
Gage et al. (2017)	United Kingdom	308,993	N.R.	21 SNPs extracted from the SCZ PGC2 GWAS, a GWAS of educational attainment by the SSGAC and the GIANT.	N.R.	N.R.	N.R.	International Cannabis Consortium, PGC2, SSGAC, GIANT and PhenoScanner.
Galvez-Buccollini et al. (2012)	USA (New York - Boston)	57	18-40 years	Individuals diagnosed with SCZ, schizoaffective disorder, schizophreniform disorder or psychosis not otherwise specified that used Cannabis before the onset of psychosis.	Male and Female	N.R.	N.R.	DIGS and FIGS.

Table 2 - *Characteristics of the studies included in the systematic review (continued).*

Study	Country	Number of participants	Age of the participants	Participants	Gender (% or *n*)	Follow-up period	Diagnostic system	Assessment tool
Gicas et al. (2021)	Canada	424	Mean= 39.6 & 43.4 years	Subjects recruited from single room occupancy hotels in the Downtown Eastside neighbourhood of Vancouver.	Male (328) and Female (96)	N.R.	DSM-4	PANSS, Time Line Follow Back Questionnaire, Hopkins Verbal Learning Test Revised, Stroop Color-Word Test, Rapid Visual Information Processing, Intra-Dimensional Extra-Dimensional Subtest, Iowa Gambling Task and MRI.
Giordano, Ohlsson, Sundquist, Sundquist, and Kendler (2015)	Sweden	5,456	< 50 years	All individuals in Sweden diagnosed with SCZ over the period 2000-2010 and individual without SCZ diagnosis from 1987 to 2010.	N.R.	N.R.	ICD	Total Population Register, Multi-Generation Register, the Swedish Hospital Discharge Register, the Out-patient CARE Register, the Swedish Crime Register and the Swedish Mortality Register.
Goldberger et al. (2010)	France	190	≥ 18 years	Male Caucasian patients with SCZ recruited from University Department of Psychiatry at Saint-Anne Hospital.	Male	N.R.	DSM-4	DIGS, PANSS, CGI, GAF and FIGS.
Gutierrez et al. (2009)	Spain	279	N.R.	Patients with SCZ diagnosis and healthy individuals.	Male (162) and Female (121)	N.R.	DSM-4	PANSS and 28-item General Health Questionnaire.
Hambrecht and Hafner (2000)	Germany	265	12-59 years	People admitted to the psychiatric hospital for the first time with a first episode of SCZ or paranoid disorder and individuals without any history of SCZ or paranoid disorder.	Male and Female	N.R.	ICD-9	IRAOS.

Table 2 - *Characteristics of the studies included in the systematic review (continued).*

Study	Country	Number of participants	Age of the participants	Participants	Gender (% or *n*)	Follow-up period	Diagnostic system	Assessment tool
Helle et al. (2016)	Norway	1,119	18-65 years	Data from the patients recruited from the Thematically Organized Psychosis Study, the Early Treatment and Intervention in Psychosis study and the Bergen Psychosis Project 2, in some areas of Norway diagnosed according to DSM-4 and screened for substance use history.	Male (688) and Female (431)	N.R.	DSM-4	SCID (modules A-E), Clinical Drug Use Scale, Clinical Alcohol Use Scale, PANSS and GAF.
Hickman, Vickerman, Macleod, Kirkbride, and Jones (2007)	United Kingdom	Birth cohorts of men and women born in 1945–49 to 1985–89	N.R.	The modelling analysis used estimates of prevalence, incidence and trends in Cannabis use derived from the Offending and Criminal Justice Survey in England and Wales from 1970-2002 and from 1945-1984.	Male and Female	32 years	N.R.	Offending Crime and Justice Survey and Computer-assisted Self-interviewing.
Hiemstra et al. (2018)	The Netherlands	372	13-20 years	Adolescents randomly selected from Secondary Schools.	Male (57%) and Female (43%)	N.R.	N.R.	Questionnaires.
Hollis et al. (2008)	United Kingdom	135	14-21 years	Participants recruited from a large-scale study, all adolescents (non-psychotic siblings of patients with adolescent-onset SCZ, healthy control adolescents and adolescents with Attention Deficit Hyperactive Disorder).	Male (70) and Female (63)	N.R.	DSM-4	SCAN, SIPS, Psychosis Screening Questionnaire, Schizotypal Personality Questionnaire, Strengths and difficulties questionnaire and GAF.

Table 2 - *Characteristics of the studies included in the systematic review (continued).*

Study	Country	Number of participants	Age of the participants	Participants	Gender (% or *n*)	Follow-up period	Diagnostic system	Assessment tool
Jain and Srivastava (2017)	India	1	18 years	Patient with history of traumatic brain injury, who later developed SCZ like symptoms soon after initiation of Cannabis use.	Male	3 years	N.R.	N.R.
James et al. (2011)	United Kingdom	60	13-18 years	Adolescents with SCZ that used Cannabis and those who didn't and healthy adolescents.	Male (40) and Female (20)	N.R.	DSM-4	K-SADS-PL, PANSS, FH-RDC, Wechsler Abbreviated Scale of Intelligence and Edinburgh Handedness Questionnaire.
Kristensen and Cadenhead (2007)	USA	48	12-30 years	Individuals at risk for SCZ.	Male and Female	2 years	DSM-4	SIPS, SCID-I, K-SADS-PL and the FH-RDC.
Kumra et al. (2012)	USA	115	10-21 years	Adolescents with early-onset SCZ, with Cannabis use disorders, both and healthy controls.	Male (61) and Female (54)	N.R.	DSM-4 & other	MRI, SCID-I, Collateral Interview, WRAT-3 Reading Subtest and CPT-IP.
Lodhi et al. (2017)	Canada	169	11-40 years	Patients with a DSM-4 diagnosis that never used Cannabis and those who did use Cannabis.	Male (119) and Female (50)	N.R.	DSM-4	Structured Clinical Interview for DSM-IV, SCID-I and Self-report Computerized Questionnaire.
Malchow et al. (2013)	Germany	77	18-40 years	Fisrt-episode SCZ patients and healthy controls.	Male and Female	N.R.	ICD-10	Structured clinical interview, PANSS, CGI, GAF, MRI and Proton Magnetic Resonance Spectroscopy
Mallet, Ramoz, Le Strat, Gorwood, and Dubertret (2017)	France	61	18-50 years	Patients with SCZ that reported heavy Cannabis use before the onset of psychosis, those who didn't report such use and those that never used Cannabis.	Male (48) and Female (13)	1 year	DSM-4-TR	CDSS, National Adult Reading Test, DIGS, PANSS, GAF, Neurological Evaluation Scale, WCST, Rey–Osterrieth Complex Figure Test, CVLT, Attention Network Test, Digit span Forward Test and the Backward digit span task.

Table 2 - *Characteristics of the studies included in the systematic review (continued).*

Study	Country	Number of participants	Age of the participants	Participants	Gender (% or *n*)	Follow-up period	Diagnostic system	Assessment tool
Manrique-Garcia et al. (2012)	Sweden	41,943	18-19 years	Swedish males that were conscripted for compulsory military service.	Male	35 years	ICD-8, ICD-9 & ICD-10	2 Non-anonymous Questionnaires, a Structured Interview, a Psychological Test and IQ Test.
Martin, Robinson, Reutens, and Mowry (2014)	Australia	633	Mean= 22.3 years	Probands and relatives with a diagnosis with SCZ or schizoaffective disorder from two consecutive studies (MGS1 (genome-wide linkage study) and MGS2 (genome-wide association study)).	Male and Female	12 months	DSM-4	DIGS, FIGS, Medical Records and Lifetime Dimensions of Psychosis Scale.
McGrath et al. (2010)	Australia	2,575	18-23 years	Women and their singleton offspring.	Male and Female	5, 14 and 21 years	ICD-10	Youth Self-Report, 21-item version of the Peters et al Delusions Inventory and CIDI.
McHugh et al. (2017)	Australia	190	14-30 years	Individuals at ultra high risk for psychosis.	Male (76) and Female (114)	Mean= 5.0 years (range 2.4-8.7 years)	DSM-4	Comprehensive assessment of at-risk mental states, GAF and SUQ.
Monteleone et al. (2014)	Italy	43	18-60 years	Patients with SCZ and healthy controls.	Male (32) and Female (11)	N.R.	DSM-4-TR	SCID-I-P (Patient edition), PANSS and Symptom Onset in Schizophrenia, Clinical Records, a Questionnaire, and Structured Clinical Interview for DSM-4-TR, non-patient edition (SCID-I-NP).
Nielsen **et al. (**2017**)**	The Netherlands	3,133,968	18-62 years	Danish population.	Male (1,618,840) and Female (1,515,128)	N.R.	ICD-8 & ICD-10	DCRS, Danish National Patient Register, DPCR, Danish National Prescription Registry, National Alcohol Treatment Register and

								National Substance Abuse Register.

Table 2 - *Characteristics of the studies included in the systematic review (continued).*

Study	Country	Number of participants	Age of the participants	Participants	Gender (% or *n*)	Follow-up period	Diagnostic system	Assessment tool
Pasman et al. (2018)	The Netherlands	184,765	16-94 years	Data from individuals of European ancestry from 16 cohorts from North America, Europe and Australia, data from the personal genetics company 23andMe Inc. and data from the UK Biobank.	Male and Female	N.R.	N.R.	GWAS, UK Biobank and 23andMe Inc..
Peters et al. (2009)	The Netherlands	56	Mean= 22.4 & 22.6 years	Male patients with SCZ, schizophreniform disorder, with schizoaffective disorder and healthy controls.	Male	N.R.	DSM-4	Longitudinal Expert Assessment of Diagnosis procedure, Annett Handedness Questionnaire and MRI.
Power et al. (2014)	Australia	2,082	Sample 1: 23-29 years; Sample 2: 18-91 years.	Healthy individuals.	Male	N.R.	N.R.	Australian Twin Registry, GWAS and Semi-Structured Assessment of the Genetics of Alcoholism.
Rodrigo et al. (2010)	Sri Lanka	3,644	11-70 years	Patients that received treatment in the Provincial General Hospital.	Male	5-9 years	ICD-10	Clinical Records and Self Report.
Roos, Pretorius, Karayiorgou, and Boraine (2006)	South Africa	341	Mean= 34.09 years	Subjects recruited by the Department of Psychiatry at the University of Pretoria.	Male (209) and Female (132)	N.R.	DSM-4	DIGS.
Sarrazin, Louppe, Doukhan, and Schurhoff (2015)	France	171	Mean= 34.0 years	SCZ subjects with and without pre-onset Cannabis use disorder.	Male (114) and Female (57)	N.R.	DSM-4-R	OCCPI, DIGS, FIGS, Montgomery and Asberg Depression Rating Scale and Beck-Rafaelson Mania Assessment Scale.

Table 2 - *Characteristics of the studies included in the systematic review (continued).*

Study	Country	Number of participants	Age of the participants	Participants	Gender (% or *n*)	Follow-up period	Diagnostic system	Assessment tool
Sevy et al. (2010)	USA (New York)	100	16-40 years	First-episode SCZ subjects with Cannabis use disorder and first-episode SCZ subjects without any substance use disorder.	Male (69) and Female (31)	3 years	DSM-4	SCID-I, Schedule for Affective Disorders and Schizophrenia Change Version with psychosis and disorganization items, SANS, Hillside Clinical Trials version of the SANS, Simpson–Angus Rating Scale, Barnes Akathisia Scale, PAS, CPT-IP, Trail Making Test, WCST, WAIS-R digit span and digit symbol, Delayed Match to Sample Task, the Set Shifting Task, CVLT, Judgment of Line Orientation, WAIS-R, Block Design Subtest, and the WRAT-3.
Shahzade, Chun, DeLisi, and Manschreck (2018)	USA (New York City & Boston)	178	18-40 years	Healthy controls with Cannabis use and SCZ patients with Cannabis use.	Male and Female	N.R.	Axis 1 Psychotic Disorder	DIGS and SIS.
Sugranyes et al. (2009)	Spain	116	15-35 years	Patients suffering from a first episode of non-affective psychosis, these patients had first-episode psychosis and subsequents diagnosis of SCZ.	Male (76) and Female (40)	1 year	DSM-4	SCID-I.
Vaucher et al. (2018)	Switzerland	79,845	N.R.	Recent and comprehensive review of the literature (published in 2016) and a meta-analysis from 2007 and 10 leading SNPs from a recent GWAS.	N.R.	N.R.	N.R.	GWAS, Mendelian Randomization analyses and Egger Mendelian Randomization.

Table 2 - *Characteristics of the studies included in the systematic review (continued).*

Study	Country	Number of participants	Age of the participants	Participants	Gender (% or *n*)	Follow-up period	Diagnostic system	Assessment tool
Veen et al. (2004)	The Netherlands	133	15-54 years	Residents who made a first-in-lifetime contact with a physician for a psychotic disorder during the time of recruitment.	Male (97) and Female (36)	N.R.	DSM-4	IRAOS and Comprehensive Assessment of Symptoms and History.
Welch et al. (2011)	United Kingdom	57	16-25 years	People at high genetic risk of SCZ at the point of entry to the EHRS.	Male (30) and Female (27)	N.R.	N.R.	EHRS and MRI.
Welch et al. (2013)	United Kingdom	55	16-25 years	People at high genetic risk of SCZ at the point of entry to the EHRS.	Male (30) and Female (25)	N.R.	N.R.	EHRS, MRI and Tensor-based morphometry.
Zammit et al. (2002)	Sweden	50,053	18-20 years	Swedish males that were conscripted for compulsory military service.	Male	27 years	ICD-8 & ICD-9	IQ Tests, Non-anonymous Questionnaires and a Structured Psychological Interview.

CARE; CDSS – Calgary Depression Scale for SCZ; CGI – Clinical Global Impression; CIDI – Composite International Diagnostic Interview; CIPD; COMT; CPT-IP – Continuous Performance Test – Identical Pairs version; CVLT – California Verbal Learning Test; DCRS – Danish Civil Registration System; DIGS – Diagnosis Interview for Genetic Studies; DPCR – Danish Psychiatric Central Register; DSM-3 – Diagnostic amd Statistical Manual of Mental Disorders, 3rd Edition; DSM-3-R – Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition Revised; DSM-4 – Diagnostic and Statistival Manual of Mental Disorders, 4th Edition; DSM-4-TR – Diagnostic amd Statistical Manual of Mental Disorders, 4th Edition, Text Revised; EHRS – Edinburgh High Risk Study; FH-RDC – Family History Research Diagnostic Criteria; FIGS – Family Interview for Genetic Studies; GAF – Global Assessment of Functioning; GIANT – Genetic Investigation of Anthropometric Traits; GWAS – Genome-wide Association Study; ICD-8; ICD-9 - International Classification of Diseases, 9th Edition; ICD-10; IQ – Intelligence Quotient; IMAGEN – Project that uses brain imaging and genetics; IRAOS – Interview for the Retrospective Assessment of the Onset of SCZ; K-SADS-PL – Kiddie Schedule for Affective Disorders and SCZ; MRI – Magnetic Resonance Imaging; OCCPI – Operational Criteria Checklist for Psychotic Illness; PANSS; PAS – Premorbid Adjustment Scale; PGC2 – Psychiatric Genetics Consortium; RDC – Research Diagnostic Criteria; SANS – Scale for Assessment of Negative Symptoms; SCAN – Schedules for Clinical Assessment in Neuropsychiatry; SCID – Structured Clinical Interview for DSM-IV; SCID-I – Structured Clinical Interview for DSM-IV Axis I Disorders; SCZ; SIPS – Structured Interview for Prodromal Symptoms; SIS – Structured Interview for Schizotypy; SNP; SSD; SSGAC – Social Science Genetics Association Consortium; SUQ – Substance Use Questionnaire; UK – United Kingdom; USA – United States of America; WAIS-R – Wechsler Adult Intelligence Scale—Revised; WCST – Wisconsin Card Sorting Test; WRAT-3 – Wide, Range Achievement Test – 3rd Edition.

Hambrecht and Hafner (2000) examined the prevalence, clinical characteristics and temporal sequence of SCZ and comorbid Cannabis abuse at early onset of psychosis, and they found that 27.5% of the first-episode schizophrenic patients have had a drug problem for over 1 year (more often over 5 years) before the first sign of SCZ. This group was named as the 'vulnerability group', which are thought to might suffer from chronic mental health deterioration caused by Cannabis.

Zammit et al. (2002) performed a follow-up study of the Andreasson et al. (1987) study, with a follow-up period of 27 years. Of 50,053 subjects, 362 were diagnosed with SCZ, 5,391 subjects (10.8%) had used Cannabis, and 73 of these (1.4%) developed SCZ. The risk of developing SCZ on Cannabis users was of 2.2 (95% CI: 1.7-2.8), and 1.5 (95% CI: 1.1-2.0) after adjustment to diagnosis at conscription, IQ score, poor social integration, disturbed behaviour, cigarette smoking, and place of upbringing. It was found a dose dependent relationship between the frequency of use of Cannabis and the risk of SCZ, with an OR of 6.7 (95% CI: 4.5-10.0) for the heaviest Cannabis users when compared to non-consumers. The association of Cannabis use and SCZ was greater in subjects admitted in the first 5 years after concription (adjusted OR=2.1; 95% CI: 1.2-3.7) compared with those admitted after 5 years (adjusted OR=1.2; 95% CI: 0.8-1.8). The frequency of the use of Cannabis was associated with SCZ in both the early onset group (adjusted OR=1.3; 95% CI: 1.1-1.6) and the later onset group (adjusted OR=1.2; 95% CI: 1.1-1.3). This study found that, in early adulthood, Cannabis use increases the risk of developing SCZ, in a dose-dependent way. Furthermore, this relation was mantained even after restricting analysis to users of only Cannabis. This study did not find a correlation between Cannabis use and other mental illnesses, impling just an increased risk of developing SCZ.

Manrique-Garcia et al. (2012) assessed the psychotic outcomes of Cannabis use in adolescence and variation in risk over time. The OR for psychotic outcomes among frequent Cannabis users compared with non-users was 3.7 (95% CI: 2.3-5.8) for SCZ, 2.2 (95% CI: 1.0-4.7) for brief psychosis, and 2.0 (95% CI: 0.8-4.7) for other non-affective psychoses. Subjects with the highest level of exposure to Cannabis had an approximately 4-fold increase in risk of developing SCZ, confirming a dose-dependent association between the frequency of use and risk of onset of the disease. The risk of SCZ declined over the decades in moderate user, but in much lesser extent in frequent users. Furthermore, the presence of a brief psychosis did not increase risk of later SCZ onset in Cannabis users compared with non-users. The findings of this study confirms there is an increased risk of SCZ in a long-term perspective, although the risk declines over time in moderate users. There is little evidence that those with a Cannabis-induced psychotic

disorder have a greater risk of transition from brief psychosic episodes to SCZ compared with non-users.

Giordano et al. (2015) used a national-level data and a co-relative control design to investigate the causal nature of the association between Cannabis abuse and the subsequent SCZ diagnosis. The authors found that the mean time between registration for Cannabis abuse and the subsequent diagnosis of SCZ was approximately 7 years and 3 months, and that Cannabis abuse was strongly associated with later SCZ diagnosis (OR=10.44; 95% CI: 8.99-12.11). This association was substantially attenuated both by increasing temporal delays between the exposure of Cannabis abuse and SCZ diagnosis, and by controlling for increasing degrees of familial confounding. Extrapolated discordant monozygotic pairs suggested that fully controlling for confounding familial factors reduced the association between the Cannabis abuse and later SCZ to more modest levels (OR of approximately 3.3 and 1.6 with 3 and 7 year temporal delays respectively). In conclusion, Cannabis abuse had an interesting causal impact on future risk for SCZ. However, the population-based estimates of Cannabis-SCZ comorbidity substantially overstimate their causal association.

Nielsen et al. (2017) investigated if the substance abuse increases the risk of developing SCZ, showing that a diagnosis of substance abuse increased the overall risk of developing SCZ (hazard ratio (HR)=6.04, 95% CI: 5.84-6.26). Cannabis and alcohol had the strongest associations (HR=5.20, 95% CI: 4.86-5.57; HR=3.38, 95% CI: 3.24-3.53, respectively). The risk was found to be significant even 10-15 years subsequent to a diagnosis of substance abuse. In conclusion, the findings show a robust association between almost any type of substance abuse and an increased risk of developing SCZ later in life.

4.2 Longitudinal studies

Arendt et al. (2005) attempted to determine whether CIPD are followed by development of persistent psychotic conditions and the timing of their onset. They showed that, in a 3 year follow-up study, a total of 238 people (44.5%) diagnosed with CIP symptoms later developed a SSD, patients with an history of CIP developed SCZ at a significantly younger age (agreeing with the findings of Veen et al. (2004)), and for the majority of patients, CIP symptoms proved to be a starting point for the development of SSD or other severe psychopathology. In another study, Arendt et al. (2008) aimed at establishing the rate ratios of developing CIP associated with predisposition to psychosis and other psychiatric disorders in a first-degree relative and comparing them with rate ratios for

developing SSD. The authors found that about half of the subjects that received treatment for CIP developed SSD within 9 years after treatment, but in terms of ratio there were no differences for those who developed SSD and other psychiatric disorders by having an history of CIP or not. So, the findings in this study indicate that CIP might not be a valid diagnosis but an early marker of SCZ.

Kristensen and Cadenhead (2007) examined the rate of use of Cannabis among participants in the Cognitive Assessment and Risk Evaluation (CARE) Program and explore the conversion of substance abuse to psychosis. After a 1 year follow-up study, 6 of 48 at-risk subjects made a transition to psychosis, and of those that became psychotic, 3 developed SCZ. It was also found that of the 32 individuals that did not use or had minimal use of Cannabis, 1 developed psychosis, while of the 16 subjects that abused or where dependent of Cannabis, 5 converted to psychosis, depicting a significant association between the abuse of Cannabis and the development of psychosis.

To determine the prevalence of substance use and its impact on outcome, Addington and Addington (2007) followed over the course of 3 years the presentation for a FEP. They found that, as the impact of Cannabis was limited to PSs, this substance may have its impact by moving an otherwise vulnerable population from an at-risk state of psychosis.

4.3 Birth cohorts studies

Degenhardt et al. (2003) wanted to model the impact of rising rates of the use of Cannabis on the incidence and prevalence of psychosis. And it was found an increase of prevalence of Cannabis in Australia with a corresponding decrease in the age of initiation of the use of Cannabis throught out the past 30 years, although there was no evidence of a significant increase in the incidence of SCZ over the same 3 decades. The data on the trends of the age of onset of SCZ also didn't show a clear pattern. The Cannabis use among people with SCZ has been found to be more common compared to the general population. So, in conclusion this study showed that the use of Cannabis does not appear to be causally related with the incidence of SCZ, since there is no evidence to say otherwise, but its use might precipitate disorders on people who are vulnerable to psychosis, and it also worsens the disorder in those who already had it.

The study of Hickman et al. (2007) aimed to estimate the long-term trends in the use of Cannabis and projections of SCZ, assuming a causal relation between the use of Cannabis and SCZ. Unfontunately they couldn't provide a direct evidence on whether the use of Cannabis causes SCZ, but appears to confirm substantial increases in the use of

Cannabis in the United Kingdom population for the last 30 years, and suggest a prolonged use initiated in younger ages. Between 1970 and 2002 the exposure to Cannabis has increased, it's incidence increased by 4-fold, the period prevalence increased by 10-fold, and its use in yougsters under 18 year old by 18-fold. But in 2010 the model projections, assuming that there is a link between SCZ and light and heavy use of Cannabis, suggest that about one-quarter of new SCZ cases could be due to the use of Cannabis, so if the association is 2-fold and only in heavy Cannabis users, then about 10% of the SCZ cases might be caused by the use of Cannabis. In conclusion, if the use of Cannabis causes SCZ, and other causes are inchanged, then an increase in both prevalence and incidence of SCZ should be apparent by 2010.

To explore the association between the use of Cannabis and psychosis-related outcomes McGrath et al. (2010) used a sibling pair analysis from a prospective birth cohort. And he found that the duration since first Cannabis use was associated with all psychosis-related outcome, and for those with of 6 or more years of duration since first Cannabis use were 2 times more likely to receive a diagnosis of nonaffective psychosis, which is having an increased risk of developing a nonaffective psychosis, they also were 4 times more likely to being the highest quartile of Peters et al Delusions Inventory score and 2 times more likely to have hallucinations. In conclusion the longer the duration since the first time using Cannabis, the higher the risk of developing a nonaffective psychosis, supporting the hypothesis that early use of Cannabis is a risk-modifying factor for psychosis-related outcomes in young adults.

4.4 Schizophrenia spectrum disorder and retrospective studies

Due to the known association between Cannabis use and SCZ, Frisher et al. (2009) assumed that the prevalence of SCZ would increase as the use of Cannabis also increases, in the United Kingdom, from 1990 onwards, but between 1996 to 2005 the incidence and prevalence of SCZ and psychoses were either stable or declining. So, this study doesn't support the specific casual link between the use of Cannabis and the incidence of psychotic disorders.

Rodrigo et al. (2010) asseesed the characteristics of the use of Cannabis and its association with SSD, they found that in the lifetime Cannabis user group, 47 patients (45.6%) were diagnosed with SSD during the follow-up, and 43 of them were diagnosed with SCZ. The relative risk of a lifetime Cannabis user to develop a SSD was 3.05 (95% CI: 2.44-3.82) compared to non-users, but when only males were considered, it was 2.91 (95% CI: 2.31-3.68). Both being statistically significant. Two of the 4 first time users

developed SSD during the follow-up. Forty three patients (91.5%) used Cannabis before the diagnosis of SSD. Seven out of the 17 of the patients diagnosed with CIP, were subsequently diagnosed with SSD. So, in conclusion lifetime Cannabis users and the male gender were significantly associated with SSD, and the use of Cannabis might be one risk factor for SSD.

To find out if subjects without pre-onset Cannabis use disorder would have a higher familial genetic liability to SCZ than SCZ subject with pre-onset Cannabis use disorder Sarrazin et al. (2015) used an Opperational Criteria Checklist for Psychotic Illness in SCZ subjects with and without pre-onset Cannabis use disorder. The author found similar results in symptoms patterns or family history between patients with and without pre-onset Cannabis use disorder. The results clearly argue against Cannabis-associated SCZ being a relevant distinct clinical entity of SCZ with specific features and does not support the hypothesis of Cannabis associated SCZ being a distinct nosographic entity.

Shahzade et al. (2018) investigated if the adolescence use of Cannabis is a risk factor for SSD, and they found that individuals that started to use Cannabis for treating psychiatric discomfort purposes began doing it earlier and had a greater associated risk than those who started for recreational purposes. It was also observed that the sedation/treatment for PSs and stimulation/treatment of NSs were positively associated with receiving an SSD diagnosis, supporting the hypothesis that motives for introductory use of Cannabis signal and increase SSD risk. The data revealed that a big contributing factor was the treatment of PSs, followed by treatment for NSs, then recreation, and finally social use, these indicates that the motives for the use of Cannabis fit a hierarchical structure, which might explain their individual contributions to SSD symptomatology. In conclusion, this study found that early use of Cannabis not only increases the overall risk, but also signals and ampliflies many of the most impairing symptoms.

4.5 Age of onset studies

Veen et al. (2004) wanted to assess the independent influences of gender and the use of Cannabis on Dutch patients with SCZ. They found that, male Cannabis users had a mean of 6.9 years younger at the illness onset than male non-users, supporting an association between the use of Cannabis and an earlier age at first psychotic episode in male SCZ patients. The median age at onset of NSs for non-users male patients was 26.5 years, while in females was 41.6 years. In Cannabis users the median age at onset of negative

symptoms was 23.7 years, while in non-users was 38.4 years. Concluding that Cannabis use was a stronger predictor than gender of age at first psychotic episode.

Roos et al. (2006) collected information from a genetic database of Afrikaners with SCZ, so that they could understand the link between the use/abuse of Cannabis and SCZ. With that information thay discovered that males with Cannabis use/abuse had an earlier age at onset of illness (22.7 years) compared to non-users/abusers males (24.4 years). So, this study concludes that Cannabis use/abuse was more common in male subjects with SCZ, and that affects the age at onset of illness. It also found that approximately half of the male SCZ subjects and a quarter of the female SCZ subjects had used or abused Cannabis.

Sugranyes et al. (2009) aimed to determine the prevalence of the use of Cannabis and to evaluate the relationship between the use of Cannabis and the age at onset of psychosis. They found that the age of the first treatment decreased as the degree of use of Cannabis increased, while post-hoc analysis showed that the use of Cannabis was associated with a decrease in age at first treatment, the mean decrease was 1.93 years. This concludes that in patients with a FEP, the age of onset of SCZ was lower in those with a Cannabis use history, also the age at onset of the disease correlated with the Cannabis use frequency. So this study agrees with others authors on the suggestion that Cannabis act as a contributing cause triggering psychosis in vulnerable individuals.

Barrigon et al. (2010) assessed the hypothesis that the use of Cannabis is associated with an earlier onset of psychosis, especially in adolescence, and they found a dose-response relationship between Cannabis age at onset of its heaviest use and the age at onset of psychosis treatment, the earlier the age at onset of its heaviest use the earlier the age at onset of psychosis treatment. After 6 months the patients were re-evaluated and 69.6% (78/112) developed SCZ. The data showed that the age at onset of psychosis treatment of patient with an history of Cannabis use 23,5 years and for patients without it was 33,5 years. The age at onset of psychosis treatment in patient with Cannabis use history was earlier than for patients without a history. In the patients that developed a non-affective psychosis, the hazard of having their FEP at a particular age had an increase by 3 in Cannabis users compared to non-users. The heaviest use in adolescence had a higher risk of an earlier age at onset of psychosis treatment compared to having its heaviest use at a later age or compared to non-users patients. This study concludes that the evidence corrobors with the catalytic role of the use of Cannabis in the onset of psychosis, since the patients with a Cannabis use history had a higher chance of having a FEP than the other patients. And it also agrees to that psychosis is caused by interaction of genetic factors and environmental events, like Cannabis use.

The purpose of the study of Sevy et al. (2010) was to determine if an earlier age at onset of PSs in SCZ was associated with a Cannabis use disorder. This study found that 75% of subjects with Cannabis use disorders had Cannabis use disorders before the onset of PSs, these subjects had an early age of onset of PSs and less motor abnormalities but more severe hallucinations and delusions compared to non Cannabis use disorder subjects, So, althought the use of Cannabis preceeded the onset of illness in most subjects, there was no significant association between the onset of illness and Cannabis use disorders. So, the findings of this study suggest that there are common risk factors for Cannabis use disorders and a poor prognosis of SCZ.

De Hert et al. (2011) wanted to investigate if the frequently reported association between the use of Cannabis and the age of onset differed as a fuction of psychiatric diagnosis, and what he found was that the use of Cannabis and a diagnosis of SCZ predicted an earlier age at onset. In 95.4% of the cases the fist Cannabis use preceded the disease onset and in the period of most intense use preceded first admission in 87.1%. So, in the end the author found that the use of Cannabis might decrease the age at onset in SCZ and reduce the effect of diagnosis, supporting the view where Cannabis use may unmask a pre-existing genetic liability that is partly shared between patients with SCZ.

Galvez-Buccollini et al. (2012) tested whether the onset of use of Cannabis had an effect on the initiation of psychosis in subjects of Boston, and it was found that, after adjusting for potential confounding factors, the age at onset of Cannabis was significantly associated with age at onset of psychosis (β=0.4, 95% CI: 0.1-0.7) and age at first hospitalization (β=0.4, 95% CI: 0.1-0.8). The mean time between the initiation of Cannabis use and the onset of psychosis was 7.0±4.3, where the most common diagnoses were SCZ and schizoaffective disorder. In conclusion, the age at onset of Cannabis is directly associated with age at onset of psychosis or age at first hospitalization, these association remain significant even after adjusting for potential confounding factors. Although Cannabis is not sufficient or necessary to trigger SCZ, but this findings are consistent with the hypothesis that Cannabis could cause or precipitate the onset of psychosis after prolonged period of time,

Donoghue et al. (2014) examined the interaction effect of gender and the use of Cannabis on age of onset of SCZ and schizoaffective disorder. And they found that Cannabis users had an ealrier age of first symptoms than non-users. The gender difference in age of onset was diminished in Cannabis smokers compared with non-Cannabis smokers. The model that includes the Cannabis use interacting with gender was the most parsimonious model, followed by the use of Cannabis alone. So, in conclusion,

the use of Cannabis is associated with an earlier age of onset of SCZ, and the gender difference in age of onset is reduced among Cannabis smokers.

Martin et al. (2014) investigated the clinical symptomatology and substance abuse rates in patients with large, rare deletions and duplications compared with SCZ patients in general. And the author found that patient with large, rare deletions had significantly less Cannabis abuse rates and an age at onset later than those without large, rare deletions. There was an interaction between Cannabis abuse, duplication status, and age at onset, with Cannabis abuse resulting in an earlier age at onset only in those without a large, rare duplication. Patients with a large, rare duplication had a later onset age for Cannabis abuse/dependence. In conclusion the SCZ patients with large, rare deletions were less likely to have comorbid Cannabis abuse over their lifetime. This findings supports a threshold model of risk with those carrying a SCZ-associated copy number variation less reliant on environmental insults. The patients with large, rare duplications were protected against earlier onset of SCZ in the presence of comorbid Cannabis abuse in addition to later onset of Cannabis abuse itself.

Helle et al. (2016) aimed to examine the relationship between the use of substance and the age at onset, in addition to the influence of possible confounders, in SSD, and to examine the effect of specific substance use, such as Cannabis and other substances, on this relationship. The patients with substance use (627) had about 3 years earlier age at onset (23.0 years) than the abstinent group (492; 25.9 years), making it a variance in age at onset of 2.9 years. Only the use of Cannabis was statistically significantly related to earlier age at onset. The findings emphasizes Cannabis as an environmental factor associated with 3 years earlier age at onset of psychosis.

Mallet et al. (2017) examined the association between the heavy use of Cannabis before the onset of psychosis and clinical, neuropsychological and neurological symptoms, including neurological soft signs. It was found that patients with heavy use of Cannabis before the onset of psychosis had significantly less neurological soft signs, less NSs and a better cognitive functioning in different domains. This study supports the clinical, neuropsychological and neurological specifcity associated with the heavy Cannabis use before the onset of SCZ. Patients with heavy use of Cannabis before the onset of SCZ might exhibit later neurodevelopmental impairment than those who do not report such use. In this group of patients, Cannabis might have played a causal role in a gene-environment interaction leading to SCZ.

4.6 Brain imaging studies

Peters et al. (2009) wanted to determine if the use of Cannabis during early adolescence was associated with white matter abnormalities in SCZ patients. They found that patients that used Cannabis before the age of 17 showed an increase directional coherence in the bilateral uncinate fasciculus, anterior internal capsule and frontal white matter, while it wasn't found in patients that didn't use Cannabis before the age of 17, making these abnormalities not related to lifetime doses of Cannabis or other illicit drugs. These findings might represent a subgroup of SCZ patients with increased white matter directional coherence, which might reflect a structural hyperconnectivity. However they couldn't determine whether the results were specifically related to the use of Cannabis before the age of 17 or the hard drug use, since there was a high overlap between the patients groups. The findings of this study might reflect an effect of Cannabis on brain development during adolescence or a direct effect of illicit drugs on the brain, it also confirms partially the hypothesis that the use of Cannabis during the early adolescence is associated with abnormalities in the white matter of SCZ patients, they also are considered as evidence for hyperconnectivity in some SCZ patients. The connectivity is the structural connections between the brain areas that is directly related to the neural communication between the areas, and hyperconnectivity means more efficient hardwiring, which results in increased functional communication. In conclusion this found an increased anisotropy in recent-onset SCZ patients with start of Cannabis use before age 17 and patients with hard drug use, it also supports the hypothesis that patients with SCZ and early illcit drug use have specific clinical characteristics, and possible different pathophysiological mechanisms, leading to both ilegal substance use and SCZ.

To test the hypothesis that the use of Cannabis in early adolescence in male patients with SCZ is related with abnormalities in white matter structure integrity, Dekker et al. (2010) used a high resolution structural and diffusion tensor brain images to compare groups of patietns. Dekker et al. (2010) found that, in patients that never used Cannabis there was reduced white matter density and reduced fractional anisotropy in the splenium of the corpus callosum compared with patients that used Cannabis before the age of 15 years. So this study shows that the age of onset of Cannabis use is not a identifiying factor for white matter abnormalities in patients with SCZ, but it also indicates that the patient that never used Cannabis have a more vulnerable brain structure.

Welch et al. (2011) examined the effects of Cannabis on longitudinal thalamus and amygdala-hippocampal complex volumes within a population at high risk of SCZ. He found that the exposure of Cannabis was related with a bilateral thalamic volume loss, this loss was significant on the left, but highly significant on the right. The effects in the amygdala-hippocampal complex were non-significant. In conclusion, this study found a reduction on the thalamic volume in a population at high familial risk of SCZ that

consumes Cannabis, but is not seen in those who are at high familial risk of SCZ that remained Cannabis-free through out the inter-scan interval. Two years later Welch et al. (2013) wanted to extend previous findings, and for that they used an automated image analysis technique to compare longitudinal brain structural changes in subjects with high risk that used or not used Cannabis during the time between the scan. Welch et al. (2013) and colleagues focused in brain regions known to be abnormal in SCZ, like hippocampi, the prefrontal lobes and the thalami, and they found that the exposure to Cannabis by individuals at elevated risk for SCZ was associated with a significantly greater loss of right anterior hippocampal and left superior frontal lobe of the grey matter. These findings remained even after the exclusion of individuals who had used other drugs during the inter-scan interval. This study demonstrates an association between Cannabis use and grey matter loss in currently well people at familial risk of developing SCZ, and it also provides evidence that, in genetically vulnerable individuals at least, the use of Cannabis is an important factor influencing regional brian volumes.

The objective of James et al. (2011) was to study the grey and whitte matter changes in patients with adolescent-onset SCZ with the early use of Cannabis and without Cannabis use versus controls. The author found that the users of Cannabis showed grey matter density loss in temporal fusiform gyrus, parahippocampal gyrus, ventral striatum, right middle temporal gyrus, insular cortex, precuneus, right paracingulate gyrus, dorsolateral prefrontal cortex, left postcentral gyrus, lateral occipital cortex and cerebellum compared with the non-users. Another comparison showed decreased fractional anisotropy in particular brain stem, internal capsule, corona radiata, superior and inferior longitudinal fasciculus in Cannabis users patients, but no cognitive differences between users and non-users, although both were impaired in comparison with controls. So, the use of Cannabis in the early adolescence increases the white and grey matter deficits in the adolescent-onset of SCZ, but doesn't increase the cognitive deficit associated with this illness.

Kumra et al. (2012) examined the bias of the comorbility of early-onset SCZ and Cannabis use disorder. They observed a significant early-onset SCZ by Cannabis use disorder interaction. In the left superior pariental region, both subjects of the early-onset SCZ and the Cannabis use disorder groups had smaller grey matter volumes that were associated with lower surface area compared with healthy controls. It was observed a similar alteration in the comorbid group compared with healthy controls, but there was no additive volumetric deficit found in the comorbid group compared with the separate groups. In the left thalamus, the comorbid group had smaller grey matter volumes compared with the Cannabis use disorder and healthy control groups. And among adolescent with pure SCZ, smaller cortical surface area in the left superior parietal cortex

was associated with worse performance on the Continuous Performance Test-Identical Pairs. In several cortical regions, Cannabis use was associated with larger brain volumes in adolescents with SCZ, but smaller brain volumes in healthy controls. In the right and left hippocampus, the use of Cannabis was associated with larger brain volumes in adolescents with SCZ, but no distinguishable effect in healthy controls. So, in conclusion, the findings indicate that the presence of Cannabis use disorder might moderate the relationship between early-onset SCZ and cerebral cortical grey matter structure in the left superior pariental lobe. They could not observe a correlation between brain volumetric measures and the timing (onset of Cannabis use) and/or quantity of Cannabis exposure.

Malchow et al. (2013) investigated the effects of previous Cannabis abuse and increased familial risk on subcortical brain regions such as hippocampus, amygdala, caudate nucleus, putamen, thalamus and subsegments of the corpus callosum. And they found that SCZ patients displayed decreased volumes of the left hippocampus, bilateral amygdala and caudate nucleus as well as an increased area of the midsagittal corpus callosum one segment of the corpus callosum compared to healthy controls. The patients that fullfilled the criteria for Cannabis abuse at admission showed an increased area of the corpus callosum two segments compared to those who did not fulfill the criteria. Patients with a family history of SCZ combined with previous Cannabis abuse as environmental factor. Patients with Cannabis abuse also had higher ratios of N-acetyl aspartate/choline in the left putamen, suggesting a possible neuroprotective effect in this area.

Gicas et al. (2021) aimed to examine how early exposure to Cannabis (by age 15) compared to later first use (after age 15) affected the expression of adult psychosis. Gicas et al. (2021) and colleagues found that early exposure to Cannabis was associated with a increased risk (OR: 1.09) of developing a substance-induced psychosis, whereas the later first use increased risk (OR: 2.19) of developing SCZ or schizophreniform disorder. There was no differences observed in the neurocognitive function, although it was observed differences in the volume of the left lateral orbitofrontal cortex (it was larger in early first users) and indices of white matter tract integrity (the later first use had increased mean and axial diffusivity in multiple pathways). All of this indicates that early exposure to Cannabis might increase the risk of developing drug associated psychoses, which could potentially be mediated in part through altered neurodevelopmental brain changes.

4.7 Physiological studies

Monteleone et al. (2014) investigated the saliva cortisol awakening response on SCZ patients onset after Cannabis exposure comparatively to patients with SCZ onset without

the exposure of Cannabis and healthy controls. This study found that SCZ patients with Cannabis exposure, the exposure ocurred from 6 months to 10 years before the onset of the illness with a frequency ranging from 1 to 4 times/week. And that SCZ patients with Cannabis exposure exhibited significantly enhanced baseline saliva cortisol levels and a flattened the cortisol awakening response. It wasn't detected a significant abnormality in both baseline cortisol levels and cortisol awakening response in SCZ patient without Cannabis exposure. All of this demonstrates a dysregulation of the hypothalamus-pituitary-adrenal axis in chronic schizophrenic patients whose illness started after the exposure of Cannabis but not in those with an illness onset without Cannabis exposure.

Bossong et al. (2015) had the objective to assess the effect of a Δ^9-THC challenge on human striatal dopamine release in a large sample of healthy participants. And, they found that the Δ^9-THC administration induced a reduction in [^{11}C]raclopride binding in the limbic striatum (-3.65%, from 2.39±0.26 to 2.30±0.23). This is consistent with increased dopamine levels in this region. There was no significant differences between Δ^9-THC and placebo were found in other striatal subdivisions. In the end, this study provides evidence for a modest increase in human striatal dopamine transmission after administration of Δ^9-THC compared to other drugs of abuse. The findings suggests a limited involvement of the ECS in regulating human striatal dopamine release and thereby challenges the hypothesis that an increase in striatal dopamine levels after Cannabis use is the primary biological mechanism underlying the associated higher risk of SCZ.

4.8 Genetic studies

Gutierrez et al. (2009) explored the possible interaction between Cannabis consumption, *COMT* gene variability and the risk of SCZ. The findings in this study supports a firm association between the consumption of Cannabis and SCZ, this association was seen in both genders, but the magnitude of the effect was greater in women. The interaction between Cannabis consumption and *COMT* gene variability in the increased risk of SCZ was only detected in women.

Estrada et al. (2011) wanted to examine whether age at first Cannabis use and age at emergence of psychiatric disorders are related, and if such a relationship is modulated by the Val158Met polymorphism in the *COMT* gene. It was found that age at the first use of Cannabis correlates with age at onset on both SCZ-spectrum and other psychiatric disorder groups, this means that those who started using Cannabis earlier had an earlier age at onset of psychiatric disorders. Another finding is that there was no difference in the distribuition of the Val158Met genotypes between the diagnosis groups or

between Cannabis users and non-users. The final finding was that it was observed an interaction between Val158Met genotypes and the use of Cannabis specifically on age at emergence of psychotic disorders, with Val/Val genotypes carriers showing an earlier age at onset than Met carriers. So, the *COMT* Val158Met genotype seems to modulate the association between Cannabis and age at onset of psychotic disorders, suggesting that the effects of Cannabis might depend on the state of brain development and maturity at the moment of first exposure. In conclusion, with this study it can be seen that although the use of Cannabis seem to have non-specific effect on the age at onset of psychiatric disorders, the modulating role of Val158Met genotypes appears to be specific to individuals with a SSD, indicating that the individuals with a SSD are more vulnerable to the effect of Cannabis on the dysregulation of their dopaminergic system than non-psychotic patients, who would be carriers of a genetic background more biologically capable to buffer these neurotransmission unbalances in the dopaminergic system.

To clarify the putative existence of Cannabis x COMT interaction in susceptibility to SCZ, Costas et al. (2011) did a case-only study and he found an association between the use of Cannabis and low activity *COMT* variants in schizophrenic patients, the joint analysis and results were consistent between the two samples based on single nucleotide polymorphisms (SNPs), haplotypes, or genotypes. This study also found that schizophrenic subjects homozygous for the Met allele at rs4680 doubled the probability of lifetime prevalence of the use of Cannabis in comparison to Val homozygous (Mantel-Haenszel OR = 2.07, 95% CI: 1.27-3.26, in the combined sample). This results agrees with the existence of an interaction of *COMT* polymorphisms and Cannabis in relation to SCZ susceptibility.

Power et al. (2014) wanted to discern the direction of causation between the use of Cannabis and SCZ. In the end he found that the polygenic risk scores for SCZ showed positive associations for Cannabis use versus never users across all P-value thresholds. So, it was found an association between an individual's burden of SCZ risk alleles and Cannabis use. The results suggest that part of the association between SCZ and Cannabis is due to a shared genetic aetiology, and it also highlights the possibility that this association might be directional in causation, and that the risks of Cannabis use could be overestimated.

French et al. (2015) investigated whether the association between the use of Cannabis and cortical maturation in adolescents is moderated by a polygenic risk score for SCZ, and he observed a negative association between the use of Cannabis in early adolescence and cortical thickness in male subjects with a high polygenic risk score. This association was not observed in low-risk male participants or for the low or high risk female subjects. In the Canadian Saguenay Youth Study male participants, the use of

Cannabis interacted with risk score vis-à-vis cortical thickness, the higher scores were associated with lower thickness only in males that used Cannabis. In the IMAGEN male subjects, the use of Cannabis interacted with an increased risk score vis-à-vis a change in decreasing cortical thickness from 14.5 to 18.5 years of age. And in the ALSPAC high-risk groups of male subjects, the ones that used Cannabis most frequently (≥61 occasions) had lower cortical thickness than those who never used Cannabis (difference in cortical thickness, 0.07 (95% CI: 0.01-0.12)) and those with light use (< 5 occasions) (difference in cortical thickness, 0.11 (95% CI: 0.03-0.18)). It is observed, due to the findings, that the use of Cannabis in early adolescence moderates the association between the genetic risk for SCZ and cortical maturation among male individuals. And implicates processes underlying cortical maturation in mediating the link between the use of Cannabis and the liability to SCZ.

Ermis et al. (2015) wanted to understand the role of Cannabis in the etiology of SCZ with and without pre-morbid usage, and for that the author compared *COMT* Val158Met polymorphism in patients with SCZ, with and without pre-morbid use of Cannabis. And found that the Val/Val genotype is significantly higher in patients with pre-morbid Cannabis use (88.9%) compared to patients without pre-morbid Cannabis use (68.4%). The mean total PANSS score seen in the Val/Val genotype group is significantly higher than the scores of the patients with the Met allele. The Val/Val genotype increases the risk of the disease by 3.69-fold. In conclusion, it was found a correlation between pre-morbid Cannabis use and COMT Val/Val genotype in patients diagnosed with SCZ. These results also support the findings of gene x environment in the Cannabis-psychosis relationship. So in the end these findings confirm the correlation between *COMT* Val158Met polymorphism and pre-morbid Cannabis use is causing SCZ.

To assess the likelihood of a causal association between the initiation of Cannabis and SCZ, Gage et al. (2017) investigated whether any association observed is due to pleiotropic effects of SNPs rather than causal effects of Cannabis on SCZ. This study found some evidence consistent with a causal effect of Cannabis initiation on risk of SCZ (OR: 1.04 per doubling odds of Cannabis initiation, 95% CI: 1.01-1.07). There was also strong evidence consistent with a causal effect of SCZ risk on likelihood of Cannabis initiation (OR: 1.10 per doubling of the odds of SCZ, 95% CI: 1.05-1.14). The results were as predicted for the negative control (height: OR: 1.00, 95% CI: 0.99-1.01) but weaker than predicted for the positive control (years in education: OR: 0.99, 95% CI: 0.97-1.00) analysis. Thus results provide some evidence that Cannabis initiation increases the risk of SCZ, although the size of the causal estimate is small. It was found a stronger evidence that SCZ risk predicts Cannabis initation, possibly as genetic instruments for SCZ are stronger than for Cannabis initiation.

Lodhi et al. (2017) investigated the association between rs4680 and age of onset of psychosis, and in those who had used Cannabis before 20 years of age, rs4680 had a trend level effect on age of onset of psychosis (mean: Val/Val (19.37) < Val/Met (20.95) < Met/Met (21.24) years). Eigthy subjects that used Cannabis before age 20 years developed an SSD and 11 that used Cannabis after age of 20 developed an SSD. The data did not indicate a significant effect, but there was a trend-level signal in the same direction as Estrada et al. (2011) study.

Aas et al. (2018) and colleagues investigated the relationship between SCZ genetic load and the use of Cannabis before the illness onset in SCZ and bipolar disorder spectrums. And for that they compared early use with later use and no use. They found that the patients with weekly to daily use of Cannabis before illness onset had the highest SCZ-polygenic risk score. The biggest difference was observed between patients with daily or weekly use of Cannabis before the illness onset before 18 years of age, and patients with no or infrequent Cannabis use. It was observed a dose relationship with the highest SCZ-polygenic risk score in the early frequent users, but intermediate in the late frequent users. Finnaly, the findings support a weak increase in SCZ-polygenic risk score in those with frequent use of Cannabis before illness onset, suggesting an overlapping genetic susceptibility. Due to this findings this study supports the existence of an association between SCZ-polygenic risk score and frequent use of Cannabis before the illness onset in psychosis continuum disorders.

Hiemstra et al. (2018) wanted to investigate how a genetic predisposition to SCZ was associated with patterns of the use of substances during adolescence, and to know that they compared the ages 13-16 years old with 16-20 years old. Hiemstra et al. (2018) and colleagues found that high SCZ vulnerability was associated with a stronger increase in Cannabis use at age 16-20 years old, whereas more lenient polygenic risk score thresholds demonstrated the reverse association. In conclusion, the results support an association between the genetic risk to SCZ and prospective use of Cannabis patterns during adolescence.

Vaucher et al. (2018) wanted to clarify the causal role of Cannabis consumption on the risk of SCZ, and for that they used a genetic approach, by taking 10 independent genetic variants previously identified to associate with the use of Cannabis, and then determine the nature of the relationship between the use of Cannabis and the risk of SCZ. They found that the use of Cannabis was associated with a increased risk of SCZ (OR of SCZ for users and non-users: 1.37, 95% CI: 1.09-1.67), and the corresponding estimate from the observational analysis was 1.43 (95% CI: 1.19-1.67). With these substantial evidence base that identified the use of Cannabis to associate with a increased risk of SCZ, they suggest that this relationship is causal.

Pasman et al. (2018) and colleagues examined whether there was evidence for a causal relationship from the use of Cannabis to SCZ risk, and from liability to SCZ to the use of Cannabis. For this they used a bi-directional two-sample Mendelian randomization analysis, and the SNP and gene-based tests revealed several SNPs and genes strongly associated with lifetime use of Cannabis, another finding, which was the strongest finding, was the Neural Cell Adhesion Molecule 1 (associated with illicit drug use, implicated in psychiatric disorders, like SCZ and mood disorders) and Cell Adhesion Molecule 2 (associated with substance use and risk-taking), They also found a positive genetic correlation between genetic risk factor for the use of Cannabis and SCZ, however there was weak evidence for a causal influence of lifetime use of Cannabis on SCZ risk, but only for the genetic instrument containing SNPs associated with the use of Cannabis under the P-value threshold 1×10^{-5}. On the other hand, they found a strong evidence for a causal positive influence of SCZ risk on lifetime use of Cannabis. In the end, this study revealed a significant SNP and gene association in 16 regions, 14 of which had not been previously implicated in the use of Cannabis, they also indicated a causal influence of liability to SCZ on the use of Cannabis and a substantial genetic overlap between the use of Cannabis and mental-health traits, personality traits, SCZ, and others.

4.9 Case report

Jain and Srivastava (2017) is the only case report included in this systematic review, and the authors wanted to see if the traumatic brain injury and the use of Cannabis use were a risk factor for the development of psychosis. The case they studied helped them to understand the common neurobiological mechanism behind SCZ and the risk factors mentioned above. This case observed a patient that started using a certain form of Cannabis at the age of 15 years, after some time this patient started using a new more potent form. After some time he went to see a psychiatrist, stopped consumming and took prescribed medicine, with this his manic symptoms improved completely. One year later, at 16 years old, a similar situation happened again and he stopped consumming and took some medicine. Each time, he stopped taking the medicine after 6 months on his own. There was no psychiatric history in his family, but this patient had a frontal lobe lesion (traumatic brain injury at the age of 3), which might be what made him develop SCZ symptoms after 1 month of using Cannabis, which persisted even after stopping the comsumption.

4.10 Other studies

Of the 757 cases in the study of Boydell et al. (2007), 182 (24%) has used Cannabis before the presentation of narrow SCZ, more males than females used Cannabis and Cannabis users were younger.

Hollis et al. (2008) examined whether adolescent at a genetic high risk of SCZ were more prone to the psychological adverse effects of Cannabis than other at low risk or others with attention deficit hyperactivity disorder. It was found a significant positive relation between the use of Cannabis and mental health disturbance in young people at a genetic high risk for SCZ that were free from prodromal or psychotic symptomatology at the time of assessment, which was not seen in healthy adolescents in the general population or in those with attention deficit hyperactivity disorder. The findings supports the view that young people at a genetic high risk for SCZ are particularly vulnerable to mental health problems associated with the use of Cannabis and are consistent with the hypothesis that there is a specific relationship between risk for SCZ and the use of Cannabis.

In a exploratory study (Buadze et al., 2010) it was examined a disease model expressed by Cannabis using patients who developed SCZ and see if they suspected a causal link between their use of Cannabis and the development of their illness. All of the patients couldn't describe a causal link between Cannabis use and their SCZ development, they even had rather positive views on Cannabis.

To know the role of individual sensitivity to the psychotogenic effect of Cannabis in male SCZ patients. Goldberger et al. (2010) interviewed male patients with SCZ, and discovered that 121 were lifetime users and 69 were non-users. Thirty-five percent of the patients used Cannabis before the onset of prodrome and 73% before the onset of PSs. Patients that used Cannabis had higher PANSS positive subscale mean scores. It wasn't found differences in age at onset of SCZ between patients with or without Cannabis use, either for age at onset of prodromal phase or for age at first psychotic episode. Of the patients that used Cannabis, 44 were classified as sensitive to the psychotogenic effects of Cannabis, while 77 were not. Twenty-three of the 44 had the onset of psychotic symptoms ocurred within 1 month after the initiation of Cannabis use following at least a 2-fold rise of the use of Cannabis, while the other 21 had marked psychotic symptoms, such as hallucinations, delusions, or disorganization, reappearing each time the patient used Cannabis. There was no age difference between the sensitives and non-sensitives. The sensitive SCZ patients had the onset of their first psychotic episode 2.6 years earlier than non-sensitives, and they also had a earlier mean age at exposure to the use of

Cannabis (1.4 years) than non-sensitives. So in conclusion the sensitivity to Cannabis was associated with family history of psychosis and age at onset of the use of Cannabis, they also had an earlier age at onset of psychosis compared to patients that used Cannabis but were not sensitive to it. It could not be found an earlier age at onset in Cannabis users comparatively to non-users. So, although Cannabis is a risk factor for SCZ, its influence is heterogenous and not all users will develop psychosis, in addition this study supports the hypothesis of a variable individual responsiveness to Cannabis that modulates the influence of Cannabis on the early course of SCZ.

McHugh et al. (2017) aimed to address the nature of the risk that Cannabis use poses, and for that they investigated how characteristics of the use of Cannabis relate to transition risk in ultra high risk populations. They also examined a novel measure of severity of Cannabis abuse as well as history of Cannabis-induced attenuated psychotic symptoms as predictors of transition risk. The results showed 28 (14.7%) of the participants transitioned to a psychotic disorder, and of these 13 met criteria for SCZ. It also showed that the history of Cannabis abuse was reported in 58% of the sample. Twenty-five percent of these reported an history of Cannabis abuse attenuated psychotic symptoms. These subjects were 4.90 (95% CI: 1.93-12.44) times more likely to transition to a psychotic disorder. They were also at 3.96 (95% CI:1.64-9.51) times greater risk of transition to a psychotic disorder than never users of Cannabis. The greater severity of Cannabis abuse predicted transition to psychosis. However, this effect was mediated by higher abuse severity among individuals with a history of Cannabis-induced attenuated psychotic symptoms. With this, it was observed that an history of Cannabis-induced attenuated psychotic symptoms in ultra high risk individuals increases dramatically the risk of transitioning to a psychotic disorder, 40% with an history developed a psychotic disorders during the follow-up. The findings suggest that Cannabis use interacts with some third unknown factor or set factors among a subpopulation of ultra high risk individuals to levate transition risk, and that this risk phenotype manifests in Cannabis-induced attenuated psychotic symptoms. The severity of Cannabis abuse only confers risk for transition to a psychotic disorder because of the enhanced severity of the abuse of Cannabis among individuals with a history of Cannabis-induced attenuated psychotic sympotms. In conclusion, these findings show an important insight into the risk posed by the use of Cannabis for individuals at ultra high risk for psychosis. They also suggest that the use of Cannabis only poses risk for a subgroup of ultra high risk individuals who also manifest Cannabis-induced attenuated psychotic symptoms.

5 Discussion

A systematic review of the available literature was conducted to assess our hypothesis that cannabinoid use may trigger the development of SCZ.

Most of the 58 studies included in our research found an association between Cannabis consumption and the onset of SCZ or at least an increased risk of development, some even described an increased risk with higher exposure to Cannabis (Aas et al., 2018; Allebeck et al., 1993; Andreasson et al., 1987; Andreasson et al., 1989; Arendt et al., 2008; Arendt et al., 2005; Bossong et al., 2015; Costas et al., 2011; Ermis et al., 2015; Gicas et al., 2021; Gutierrez et al., 2009; Hiemstra et al., 2018; James et al., 2011; Kumra et al., 2012; Mallet et al., 2017; Manrique-Garcia et al., 2012; Monteleone et al., 2014; Pasman et al., 2018; Shahzade et al., 2018; Vaucher et al., 2018; Zammit et al., 2002). Some works found such association only in vulnerable individuals (Addington & Addington, 2007; De Hert et al., 2011; Degenhardt et al., 2003; Estrada et al., 2011; Goldberger et al., 2010; Hambrecht & Hafner, 2000; Hollis et al., 2008; Lodhi et al., 2017; Martin et al., 2014; Peters et al., 2009; Power et al., 2014; Welch et al., 2013; Welch et al., 2011). Six studies found that Cannabis use was associated with an early onset of SCZ compared to non-users SCZ (Donoghue et al., 2014; Galvez-Buccollini et al., 2012; Helle et al., 2016; Roos et al., 2006; Sugranyes et al., 2009; Veen et al., 2004). Two studies found an association between the consumption of Cannabis and psychosis, although not all subjects were diagnosed with SCZ later on (Barrigon et al., 2010; Kristensen & Cadenhead, 2007). One study by Rodrigo et al. (2010) showed that Cannabis is one of many risk factors for the development of an SSD, while another study found a reverse association, where SCZ leads to Cannabis consumption initiation (Gage et al., 2017). There was a study where most subjects used Cannabis before the onset of SCZ, but they authors found no significant association between the onset of SCZ and drug abuse (Sevy et al., 2010). Another work found that the consumption of any substance of abuse is associated with an increased risk of developing SCZ later in life (Nielsen et al., 2017). In the case report published by Jain and Srivastava (2017), the authors concluded that Cannabis consumption on a patient with a traumatic brain injury prompted a rapid development of SCZ-like symptoms. One study supports that the use of early use of Cannabis is a risk factor for psychosis-related outcomes in young adults (McGrath et al., 2010), and another found that, only in vulnerable individuals, Cannabis use could lead to psychosis (McHugh et al., 2017). Only 6 studies could not find an association between Cannabis use and SCZ (Buadze et al., 2010; Dekker et al., 2010; Frisher et al., 2009; Giordano et al., 2015; Hickman et al., 2007; Sarrazin et al., 2015). In terms of

physiological pathways, Malchow et al. (2013) found that patients with Cannabis abuse had higher ratios of N-acetyl aspartate/choline in the left putamen, suggesting a possible neuroprotective effect in this area. French et al. (2015) found that the use of Cannabis in early adolescence moderates the association between the genetic risk for SCZ and cortical maturation among male individuals and implicates processes underlying cortical maturation in mediating the link between the use of Cannabis and the liability to SCZ.

Taken together, data from the 58 studies analysed substantiate a key role of Cannabis abuse in the onset of SCZ, either as an actual trigger or at least as a potentiating factor. Nonetheless, the mechanisms underlying this interaction are still poorly understood, and require further assessment.

As far as we know, this systematic review comprises an unique set of exclusion and inclusion criteria, differentiating it from other published systematic reviews on this matter. But similar studies have been published throught out the years, such as systematic reviews that associate the ECS and its role in SCZ, as well the CNR1 gene in SCZ (Ferretjans, Moreira, Teixeira, & Salgado, 2012; Gouvea et al., 2017). The majority of systematic reviews existing to this day approach the association between Cannabis and psychosis in general, and not particularly SCZ (Marconi, Di Forti, Lewis, Murray, & Vassos, 2016; Semple et al., 2005; Uliana et al., 2013). So, the present study was conducted to specify the correlation between the use of Cannabis and SCZ at different levels, comprising from national cohort studies to genetic studies. Aditionally, other systematic reviews usually tackle a particular characteristic of this association, such as the age of onset of SCZ and brain effects in adolescents, or are even conducted over other systematic reviews and meta-analysis (Hasan et al., 2020; James, James, & Thwaites, 2013; Myles, Newall, Nielssen, & Large, 2012; Patel, Khan, M, & Hamid, 2020). The closest systematic review to this study is the one performed by van der Steur, Batalla, and Bossong (2020), which has an equal broadness, but it is not specific to SCZ, approaching Cannabis use and the onset of psychosis.

Despite the novelty of the work, it does not come without its limitations. The main limitation is that all steps implicated in the process of sellecting the studies to be inlcuded in the analyses (from searching, collecting, reading and excluding publications) was done by a single person, which increases the probabily of ocurrence of errors, such as mistankingly excluding eligible publications.

The temporal association between Cannabis exposure and the development of SCZ is a complicated factor to study, due to the difficulty to accurately determine the onset of the disease. The best point of reference might be the onset of PSs, like delusions, hallucinations, or disorganization, although some argue that the onset of prodrome is a more valid starting point for the study of causality, since it represents a

period of distinct changes that later are identified as early signs of an emerging disorder (Ramsay & Compton, 2011). Moreover, the widely recognized phenomenological, and likely etiologic, heterogeneity of SSD imposes another important limiting factor for this type of causality studies (Ramsay & Compton, 2011).

The Cannabis plant contains varying levels of diverse constituents, and some of them have opposite effects, like Δ^9-THC and CBD, making it important to study the effects of specific phytocannabinoids, as their contribution will most likely have different implications in association of Cannabis and psychosis (Ramsay & Compton, 2011).

The continued research on the ECS, the naturally occurring or synthetic agents that interact with this system will lead to many advances in the understanding of this complex link between the use of cannabinoid abuse and psychotic disorders (Ramsay & Compton, 2011).

On the other hand, the use of Cannabis specifically in early adolescence is generally considered a cause component of SSD, but more research is needed to understand other potential directions of causality, like how psychotic symptoms may lead to the initiation or escalation of the use of Cannabis (Ramsay & Compton, 2011).

Considering all gathered information, there is a great need to develop more effective interventions for the treatment of Cannabis-related disorders, especially targeting those who are predisposed to SCZ and related psychotic disorders (Ramsay & Compton, 2011). As adolescence or premorbid use of Cannabis appears to potentiate SSD, different authors suggested prevention measures (Ramsay & Compton, 2011). Arseneault et al. (2004a) stated that even though most of the young people that use Cannabis do it without serious consequences, there is a vulnerable minority that will experience harmful outcomes and that the use of Cannabis among psychological vulnerable young adolescents should be firmly discouraged by the parents, the teachers, and the health professionals. The authors also acknowledged that the policy-makers should be concentrating on public health measures to delay the initiation of the use of Cannabis since the youngest users of Cannabis appear to be more at risk (Arseneault et al., 2002). Moore et al. (2007) further considered that there is enough evidence to warn young people that Cannabis use could increase the risk of developing psychotic illness in the future, asserting that, although the risk of developing a psychotic disorder from cannabinoid abuse is likely to be low, it may a have substantial effect at a global level, considering the widespread use of Cannabis. Additionally, the possibility of delaying the onset of psychosis by reducing premorbid or prodromal use of Cannabis in those at high genetic or psychometric risk might also have a significant impact in disease outcome (Ramsay & Compton, 2011).

6 Conclusion

Through the present work, we can conclude that cannabinoid abuse is more than likely to be associated to the onset of SCZ, as confirmed by the majority of the studies included in the present systematic review. However, more studies are needed to know what are the underlying mechanisms, and what factors, either genetic or environmental, may be involved in this association.

Since SCZ has a high morbidity and mortality, it is important to fully understand to which degree cannabinoid substances abuse have the ability to potentiate or trigger such disorders, and correctly inform the population of these findings, discouraging them to use these type of substances. It also important that the Government takes effective actions regarding this issue, by creating and applying control measures that contribute to reducing and/or preventing the use of Cannabis and SCs.

7 References

Aas, M., Melle, I., Bettella, F., Djurovic, S., Le Hellard, S., Bjella, T., . . . Tesli, M. (2018). Psychotic patients who used cannabis frequently before illness onset have higher genetic predisposition to schizophrenia than those who did not. *Psychological Medicine, 48*(1), 43-49. doi:10.1017/S0033291717001209

Addington, J., & Addington, D. (2007). Patterns, predictors and impact of substance use in early psychosis: a longitudinal study. *Acta Psychiatrica Scandinavica, 115*(4), 304-309. doi:10.1111/j.1600-0447.2006.00900.x

Adler, L. E., Pachtman, E., Franks, R. D., Pecevich, M., Waldo, M. C., & Freedman, R. (1982). Neurophysiological evidence for a defect in neuronal mechanisms involved in sensory gating in schizophrenia. *Biological Psychiatry, 17*(6), 639-654. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/7104417

Aldington, S., Williams, M., Nowitz, M., Weatherall, M., Pritchard, A., McNaughton, A., . . . Beasley, R. (2007). Effects of cannabis on pulmonary structure, function and symptoms. *Thorax, 62*(12), 1058-1063. doi:10.1136/thx.2006.077081

Allebeck, P., Adamsson, C., Engstrom, A., & Rydberg, U. (1993). Cannabis and schizophrenia: a longitudinal study of cases treated in Stockholm County. *Acta Psychiatrica Scandinavica, 88*(1), 21-24. doi:10.1111/j.1600-0447.1993.tb03408.x

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders: DSM-5.*(5th ed., pp. 87-123).

Andreasen, N. C. (2000). Schizophrenia: the fundamental questions. *Brain Research: Brain Research Reviews, 31*(2-3), 106-112. doi:10.1016/s0165-0173(99)00027-2

Andreasson, S., Allebeck, P., Engstrom, A., & Rydberg, U. (1987). Cannabis and schizophrenia. A longitudinal study of Swedish conscripts. *Lancet, 2*(8574), 1483-1486. doi:10.1016/s0140-6736(87)92620-1

Andreasson, S., Allebeck, P., & Rydberg, U. (1989). Schizophrenia in users and nonusers of cannabis. A longitudinal study in Stockholm County. *Acta Psychiatrica Scandinavica, 79*(5), 505-510. doi:10.1111/j.1600-0447.1989.tb10296.x

Arendt, M., Mortensen, P. B., Rosenberg, R., Pedersen, C. B., & Waltoft, B. L. (2008). Familial predisposition for psychiatric disorder: comparison of subjects treated for cannabis-induced psychosis and schizophrenia. *Archives of General Psychiatry, 65*(11), 1269-1274. doi:10.1001/archpsyc.65.11.1269

Arendt, M., Rosenberg, R., Foldager, L., Perto, G., & Munk-Jorgensen, P. (2005). Cannabis-induced psychosis and subsequent schizophrenia-spectrum disorders: follow-up study of 535 incident cases. *The British Journal of Psychiatry, 187*, 510-515. doi:10.1192/bjp.187.6.510

Arseneault, L., Cannon, M., Poulton, R., Murray, R., Caspi, A., & Moffitt, T. E. (2002). Cannabis use in adolescence and risk for adult psychosis: longitudinal prospective study. *BMJ, 325*(7374), 1212-1213. doi:10.1136/bmj.325.7374.1212

Arseneault, L., Cannon, M., Witton, J., & Murray, R. (2004a). Cannabis as a potential casual factor in schizophrenia. In D. Castle & R. Murray (Eds.), *Marijuana and madness: Psychiatry and neurobiology* (pp. 101-118). Cambridge: Cambridge University Press. doi:10.1017/CBO9780511543630.009

Arseneault, L., Cannon, M., Witton, J., & Murray, R. M. (2004b). Causal association between cannabis and psychosis: examination of the evidence. *The British Journal of Psychiatry, 184*, 110-117. doi:10.1192/bjp.184.2.110

Ashtari, M., Cervellione, K., Cottone, J., Ardekani, B. A., Sevy, S., & Kumra, S. (2009). Diffusion abnormalities in adolescents and young adults with a history of heavy cannabis use. *Journal of Psychiatric Research, 43*(3), 189-204. doi:10.1016/j.jpsychires.2008.12.002

Ashton, C. H. (2001). Pharmacology and effects of cannabis: a brief overview. *The British Journal of Psychiatry, 178(2)*, 101–106.

Baggelaar, M. P., Maccarrone, M., & van der Stelt, M. (2018). 2-Arachidonoylglycerol: A signaling lipid with manifold actions in the brain. *Progress in Lipid Research, 71*, 1-17. doi:10.1016/j.plipres.2018.05.002

Bailey, E. L., & Swallow, B. L. (2004). The relationship between cannabis use and schizotypal symptoms. *European Psychiatry, 19*(2), 113-114. doi:10.1016/j.eurpsy.2003.12.001

Banister, S. D., Moir, M., Stuart, J., Kevin, R. C., Wood, K. E., Longworth, M., . . . Kassiou, M. (2015). Pharmacology of Indole and Indazole Synthetic Cannabinoid Designer Drugs AB-FUBINACA, ADB-FUBINACA, AB-PINACA, ADB-PINACA, 5F-AB-PINACA, 5F-ADB-PINACA, ADBICA, and 5F-ADBICA. *ACS Chemical Neuroscience, 6*(9), 1546-1559. doi:10.1021/acschemneuro.5b00112

Barnes, T. R., Mutsatsa, S. H., Hutton, S. B., Watt, H. C., & Joyce, E. M. (2006). Comorbid substance use and age at onset of schizophrenia. *The British Journal of Psychiatry, 188*, 237-242. doi:10.1192/bjp.bp.104.007237

Barnett-Norris, J., Hurst, D. P., Lynch, D. L., Guarnieri, F., Makriyannis, A., & Reggio, P. H. (2002). Conformational memories and the endocannabinoid binding site at the cannabinoid CB1 receptor. *Journal of Medicinal Chemistry, 45*(17), 3649-3659. doi:10.1021/jm0200761

Barrales-Cureño, H. J., López-Valdez, L. G., Reyes, C., Cetina-Alcalá, V. M., Vasquez-García, I., Diaz-Lira, O. F., & Herrera-Cabrera, B. E. (2020). Chemical Characteristics, Therapeutic Uses, and Legal Aspects of the Cannabinoids of Cannabis sativa: A Review. *Brazilian Archives of Biology and Technology, 63*. doi:10.1590/1678-4324-2020190222

Barrigon, M. L., Gurpegui, M., Ruiz-Veguilla, M., Diaz, F. J., Anguita, M., Sarramea, F., & Cervilla, J. (2010). Temporal relationship of first-episode non-affective psychosis with cannabis use: a clinical verification of an epidemiological hypothesis. *Journal of Psychiatric Research, 44*(7), 413-420. doi:10.1016/j.jpsychires.2009.10.004

Barta, P. E., Pearlson, G. D., Powers, R. E., Richards, S. S., & Tune, L. E. (1990). Auditory hallucinations and smaller superior temporal gyral volume in schizophrenia. *American Journal of Psychiatry, 147*(11), 1457-1462. doi:10.1176/ajp.147.11.1457

Bebbington, P. E., Bhugra, D., Brugha, T., Singleton, N., Farrell, M., Jenkins, R., . . . Meltzer, H. (2004). Psychosis, victimisation and childhood disadvantage: evidence from the second British National Survey of Psychiatric Morbidity. *The British Journal of Psychiatry, 185*, 220-226. doi:10.1192/bjp.185.3.220

Berdyshev, E. V., Boichot, E., & Lagente, V. (1996). Anandamide--a new look on fatty acid ethanolamides. *Journal of Lipid Mediators and Cell Signalling, 15*(1), 49-67. doi:10.1016/s0929-7855(96)00548-2

Berrendero, F., Sepe, N., Ramos, J. A., Di Marzo, V., & Fernandez-Ruiz, J. J. (1999). Analysis of cannabinoid receptor binding and mRNA expression and endogenous cannabinoid contents in the developing rat brain during late gestation and early postnatal period. *Synapse, 33*(3), 181-191. doi:10.1002/(SICI)1098-2396(19990901)33:3<181::AID-SYN3>3.0.CO;2-R

Bersani, G., Orlandi, V., Gherardelli, S., & Pancheri, P. (2002). Cannabis and neurological soft signs in schizophrenia: absence of relationship and influence on psychopathology. *Psychopathology, 35*(5), 289-295. doi:10.1159/000067064

Bhattacharyya, S., Fusar-Poli, P., Borgwardt, S., Martin-Santos, R., Nosarti, C., O'Carroll, C., . . . McGuire, P. (2009). Modulation of mediotemporal and ventrostriatal function in humans by Δ9- tetrahydrocannabinol. *Archives of General Psychiatry, 66(4)*, 442-451. Retrieved from http://public-files.prbb.org/publicacions/02901180-d615-012d-a82e-000c293b26d5.pdf

Boggs, D. L., Nguyen, J. D., Morgenson, D., Taffe, M. A., & Ranganathan, M. (2018). Clinical and Preclinical Evidence for Functional Interactions of Cannabidiol and Delta(9)-Tetrahydrocannabinol. *Neuropsychopharmacology, 43*(1), 142-154. doi:10.1038/npp.2017.209

Bonfa, L., Vinagre, R. C., & de Figueiredo, N. V. (2008). Cannabinoids in chronic pain and palliative care. *Revista Brasileira de Anestesiologia, 58*(3), 267-279. doi:10.1590/s0034-70942008000300010

Bossong, M. G., Mehta, M. A., van Berckel, B. N., Howes, O. D., Kahn, R. S., & Stokes, P. R. (2015). Further human evidence for striatal dopamine release induced by administration of 9-tetrahydrocannabinol (THC): selectivity to limbic striatum. *Psychopharmacology (Berl), 232*(15), 2723-2729. doi:10.1007/s00213-015-3915-0

Bossong, M. G., van Berckel, B. N., Boellaard, R., Zuurman, L., Schuit, R. C., Windhorst, A. D., . . . Kahn, R. S. (2009). Delta 9-tetrahydrocannabinol induces dopamine release in the human striatum. *Neuropsychopharmacology, 34*(3), 759-766. doi:10.1038/npp.2008.138

Bossong, M. G., van Hell, H. H., Schubart, C. D., van Saane, W., Iseger, T. A., Jager, G., . . . Ramsey, N. F. (2019). Acute effects of 9-tetrahydrocannabinol (THC) on resting state brain function and their modulation by COMT genotype. *European Neuropsychopharmacology, 29*(6), 766-776. doi:10.1016/j.euroneuro.2019.03.010

Bouaboula, M., Rinaldi, M., Carayon, P., Carillon, C., Delpech, B., Shire, D., . . . Casellas, P. (1993). Cannabinoid-receptor expression in human leukocytes. *European Journal of Biochemistry, 214*(1), 173-180. doi:10.1111/j.1432-1033.1993.tb17910.x

Bow, E. W., & Rimoldi, J. M. (2016). The Structure-Function Relationships of Classical Cannabinoids: CB1/CB2 Modulation. *Perspectives in Medicinal Chemistry, 8*, 17-39. doi:10.4137/PMC.S32171

Boydell, J., Dean, K., Dutta, R., Giouroukou, E., Fearon, P., & Murray, R. (2007). A comparison of symptoms and family history in schizophrenia with and without prior cannabis use: implications for the concept of cannabis psychosis. *Schizophrenia Research, 93*(1-3), 203-210. doi:10.1016/j.schres.2007.03.014

Brown, J. D., Rivera Rivera, K. J., Hernandez, L. Y. C., Doenges, M. R., Auchey, I., Pham, T., & Goodin, A. J. (2021). Natural and Synthetic Cannabinoids: Pharmacology, Uses, Adverse Drug Events, and Drug Interactions. *The Journal of Clinical Pharmacology, 61 Suppl 2*, S37-S52. doi:10.1002/jcph.1871

Buadze, A., Stohler, R., Schulze, B., Schaub, M., & Liebrenz, M. (2010). Do patients think cannabis causes schizophrenia? - A qualitative study on the causal beliefs of cannabis using patients with schizophrenia. *Harm Reduction Journal, 7*, 22. doi:10.1186/1477-7517-7-22

Bulbena-Cabre, A., DiGenova, P., Sigel, P., Dunn, N. R., & Swift, R. G. (2018). Synthetic cannabinoid intoxication presenting as malignant catatonia: A case report. *International Journal of Mental Health and Addiction*, 1–5. doi:10.1007/s11469-018-9954-0

Casadio, P., Fernandes, C., Murray, R. M., & Di Forti, M. (2011). Cannabis use in young people: the risk for schizophrenia. *Neuroscience & Biobehavioral Reviews, 35*(8), 1779-1787. doi:10.1016/j.neubiorev.2011.04.007

Casarella, J. (2020). What Is a Psychotic Disorder? Retrieved from https://www.webmd.com/schizophrenia/guide/mental-health-psychotic-disorders. Access: 11/9/2021

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. doi:10.1016/j.biopsych.2005.01.026

Castaneto, M. S., Gorelick, D. A., Desrosiers, N. A., Hartman, R. L., Pirard, S., & Huestis, M. A. (2014). Synthetic cannabinoids: epidemiology, pharmacodynamics, and clinical implications. *Drug and Alcohol Dependence, 144*, 12-41. doi:10.1016/j.drugalcdep.2014.08.005

Castle, D. J., & Solowij, N. (2004). Acute and subacute psychomimetic effects of cannabis in humans. In D. Castle & R. Murray (Eds.), *Marijuana and madness: psychiatry and neurobiology.* (pp. 41–53). Cambridge: Cambridge University Press.

Caton, C. L., Hasin, D. S., Shrout, P. E., Drake, R. E., Dominguez, B., First, M. B., . . . Schanzer, B. (2007). Stability of early-phase primary psychotic disorders with concurrent substance use and substance-induced psychosis. *The British Journal of Psychiatry, 190*, 105-111. doi:10.1192/bjp.bp.105.015784

Center for Behavioral Health Statistics and Quality. (2016). *Impact of the DSM-IV to DSM-5 Changes on the National Survey on Drug Use and Health.* Retrieved from Rockville, MD: https://www.ncbi.nlm.nih.gov/books/NBK519697/

Charlson, F. J., Ferrari, A. J., Santomauro, D. F., Diminic, S., Stockings, E., Scott, J. G., . . . Whiteford, H. A. (2018). Global Epidemiology and Burden of Schizophrenia: Findings From the Global Burden of Disease Study 2016. *Schizophrenia Bulletin, 44*(6), 1195-1203. doi:10.1093/schbul/sby058

Chicca, A., Schafroth, M. A., Reynoso-Moreno, I., Erni, R., Petrucci, V., Carreira, E. M., & Gertsch, J. (2018). Uncovering the psychoactivity of a cannabinoid from liverworts associated with a legal high. *Science Advances, 4*(10), eaat2166. doi:10.1126/sciadv.aat2166

Clarke, M. C., Harley, M., & Cannon, M. (2006). The role of obstetric events in schizophrenia. *Schizophrenia Bulletin, 32*(1), 3-8. doi:10.1093/schbul/sbj028

Compton, M. T., Kelley, M. E., Ramsay, C. E., Pringle, M., Goulding, S. M., Esterberg, M. L., . . . Walker, E. F. (2009). Association of pre-onset cannabis, alcohol, and tobacco use with age at onset of prodrome and age at onset of psychosis in first-episode patients. *American Journal of Psychiatry, 166*(11), 1251-1257. doi:10.1176/appi.ajp.2009.09030311

Compton, M. T., & Ramsay, C. E. (2009). The impact of pre-onset cannabis use on age at onset of prodromal and psychotic symptoms. *Primary Psychiatry, 16(4)*, 35-43.

Condie, R., Herring, A., Koh, W. S., Lee, M., & Kaminski, N. E. (1996). Cannabinoid inhibition of adenylate cyclasemediated signal transduction and interleukin 2 (IL-2) expression in the murine T-cell line, EL4.IL-2. *Journal of Biological Chemistry, 271*, 13175-13183.

Cooper, Z. D., & Haney, M. (2009). Comparison of subjective, pharmacokinetic, and physiological effects of marijuana smoked as joints and blunts. *Drug and Alcohol Dependence, 103(3)*, 107-113.

Copeland, J., Rooke, S., & Swift, W. (2013). Changes in cannabis use among young people: impact on mental health. *Current Opinion in Psychiatry, 26*(4), 325-329. doi:10.1097/YCO.0b013e328361eae5

Costas, J., Sanjuan, J., Ramos-Rios, R., Paz, E., Agra, S., Tolosa, A., . . . Arrojo, M. (2011). Interaction between COMT haplotypes and cannabis in schizophrenia: a case-only study in two samples from Spain. *Schizophrenia Research, 127*(1-3), 22-27. doi:10.1016/j.schres.2011.01.014

Crebbin, K., Mitford, E., Paxton, R., & Turkington, D. (2009). First-episode drug-induced psychosis: a medium term follow up study reveals a high-risk group. *Social Psychiatry and Psychiatric Epidemiology, 44*(9), 710-715. doi:10.1007/s00127-008-0490-2

Cristino, L., Bisogno, T., & Di Marzo, V. (2020). Cannabinoids and the expanded endocannabinoid system in neurological disorders. *Nature Reviews Neurology, 16*(1), 9-29. doi:10.1038/s41582-019-0284-z

Cutting, J. (2015). First rank symptoms of schizophrenia: their nature and origin. *History of Psychiatry, 26*(2), 131-146. doi:10.1177/0957154X14554369

D'Souza, D. C., Abi-Saab, W. M., Madonick, S., Forselius-Bielen, K., Doersch, A., Braley, G., . . . Krystal, J. H. (2005). Delta-9-tetrahydrocannabinol effects in schizophrenia: implications for cognition, psychosis, and addiction. *Biological Psychiatry, 57*(6), 594-608. doi:10.1016/j.biopsych.2004.12.006

D'Souza, D. C., Cho, H.-S., Perry, E. B., & Krystal, J. H. (2004). Cannabinoid 'model' psychosis, dopamine—cannabinoid interactions and implicationsfor schizophrenia. In D. Castle & R. Murray (Eds.), *Marijuana and madness: Psychiatry and neurobiology.* (pp. 142–165): Cambridge University Press. doi:10.1017/CBO9780511543630.012

D'Souza, D. C., Perry, E., MacDougall, L., Ammerman, Y., Cooper, T., Wu, Y. T., . . . Krystal, J. H. (2004). The psychotomimetic effects of intravenous delta-9-tetrahydrocannabinol in healthy individuals: implications for psychosis. *Neuropsychopharmacology, 29*(8), 1558-1572. doi:10.1038/sj.npp.1300496

D'Souza, D. C., Radhakrishnan, R., Sherif, M., Cortes-Briones, J., Cahill, J., Gupta, S., . . . Ranganathan, M. (2016). Cannabinoids and Psychosis. *Current Pharmaceutical Design, 22*(42), 6380-6391. doi:10.2174/1381612822666160826105628

D'Souza, D. C., Sewell, R. A., & Ranganathan, M. (2009). Cannabis and psychosis/schizophrenia: human studies. *European Archives of Psychiatry and Clinical Neuroscience, 259*(7), 413-431. doi:10.1007/s00406-009-0024-2

Davis, M. P. (2014). Cannabinoids in pain management: CB1, CB2 and non-classic receptor ligands. *Expert Opinion on Investigational Drugs, 23*(8), 1123-1140. doi:10.1517/13543784.2014.918603

De Hert, M., Wampers, M., Jendricko, T., Franic, T., Vidovic, D., De Vriendt, N., . . . van Winkel, R. (2011). Effects of cannabis use on age at onset in schizophrenia and bipolar disorder. *Schizophrenia Research, 126*(1-3), 270-276. doi:10.1016/j.schres.2010.07.003

De Petrocellis, L., Ligresti, A., Moriello, A. S., Allara, M., Bisogno, T., Petrosino, S., . . . Di Marzo, V. (2011). Effects of cannabinoids and cannabinoid-enriched Cannabis extracts on TRP channels and endocannabinoid metabolic enzymes. *British Journal of Pharmacology, 163*(7), 1479-1494. doi:10.1111/j.1476-5381.2010.01166.x

Dean, B., Sundram, S., Bradbury, R., Scarr, E., & Copolov, D. (2001). Studies on [3H]CP-55940 binding in the human central nervous system: regional specific changes in density of cannabinoid-1 receptors associated with schizophrenia and cannabis use. *Neuroscience, 103*(1), 9-15. doi:10.1016/s0306-4522(00)00552-2

Degenhardt, F., Stehle, F., & Kayser, O. (2017). The Biosynthesis of Cannabinoids. In Preedy V. R. (Ed.), *Handbook of Cannabis and Related Pathologies: Biology, Pharmacology, Diagnosis, and Treatment.* (1st ed., pp. 13-23): Academic Press. doi:10.1016/B978-0-12-800756-3.00002-8

Degenhardt, L., Hall, W., & Lynskey, M. (2001). Comorbidity between cannabis use and psychosis: modeling some possible relationships. *National Drug and Alcohol Research Center* (No. 121).

Degenhardt, L., Hall, W., & Lynskey, M. (2003). Testing hypotheses about the relationship between cannabis use and psychosis. *Drug and Alcohol Dependence, 71*(1), 37-48. doi:10.1016/s0376-8716(03)00064-4

Dekker, N., Meijer, J., Koeter, M., van den Brink, W., van Beveren, N., Kahn, R. S., . . . Investigators, G. (2012). Age at onset of non-affective psychosis in relation to cannabis use, other drug use and gender. *Psychological Medicine, 42*(9), 1903-1911. doi:10.1017/S0033291712000062

Dekker, N., Schmitz, N., Peters, B. D., van Amelsvoort, T. A., Linszen, D. H., & de Haan, L. (2010). Cannabis use and callosal white matter structure and integrity in recent-onset schizophrenia. *Psychiatry Research, 181*(1), 51-56. doi:10.1016/j.pscychresns.2009.06.003

Delisi, L. E., Bertisch, H. C., Szulc, K. U., Majcher, M., Brown, K., Bappal, A., & Ardekani, B. A. (2006). A preliminary DTI study showing no brain structural change associated with adolescent cannabis use. *Harm Reduction Journal, 3*, 17. doi:10.1186/1477-7517-3-17

Devane, W. A., Dysarz, F. A., 3rd, Johnson, M. R., Melvin, L. S., & Howlett, A. C. (1988). Determination and characterization of a cannabinoid receptor in rat brain. *Molecular Pharmacology, 34*(5), 605-613. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/2848184

Dharmapuri, S., Miller, K., & Klein, J. D. (2020). Marijuana and the Pediatric Population. *Pediatrics, 146*(2). doi:10.1542/peds.2019-2629

Di Forti, M., Iyegbe, C., Sallis, H., Kolliakou, A., Falcone, M. A., Paparelli, A., . . . Murray, R. M. (2012). Confirmation that the AKT1 (rs2494732) genotype influences the risk of psychosis in cannabis users. *Biological Psychiatry, 72*(10), 811-816. doi:10.1016/j.biopsych.2012.06.020

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. *Lancet Psychiatry, 2*(3), 233-238. doi:10.1016/S2215-0366(14)00117-5

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. doi:10.1192/bjp.bp.109.064220

Di Forti, M., & Murray, R. M. (2005). Cannabis consumption and risk of developing schizophrenia: myth or reality? *Epidemiologia e Psichiatria Sociale, 14*(4), 184-187. doi:10.1017/s1121189x00007922

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. doi:10.1093/schbul/sbt181

Di Marzo, V. (2008). CB(1) receptor antagonism: biological basis for metabolic effects. *Drug Discovery Today, 13*(23-24), 1026-1041. doi:10.1016/j.drudis.2008.09.001

Di Marzo, V., Bifulco, M., & De Petrocellis, L. (2004). The endocannabinoid system and its therapeutic exploitation. *Nature Reviews Drug Discovery, 3*(9), 771-784. doi:10.1038/nrd1495

Di Marzo V., & Wang J. (2014). *The Endocannabinoidome: The World of Endocannabinoids and Related Mediators.* (Di Marzo V. & Wang J. Eds. 1st ed.). Cambridge, MA: Academic Press.

Diao, X., & Huestis, M. A. (2019). New Synthetic Cannabinoids Metabolism and Strategies to Best Identify Optimal Marker Metabolites. *Frontiers in Chemistry, 7*, 109. doi:10.3389/fchem.2019.00109

Dittrich, A., & Woggon, B. (1972). Subjective syndromes, physiological changes and after-effectsof the acute ∆9-Tetrahydrocannabinol intoxication: two double-blind studies in volunteers. *European Archives of Psychiatry and Clinical Neuroscience, 263(3)*, 301-309.

Donato, H., & Donato, M. (2019). [Stages for Undertaking a Systematic Review]. *Acta Médica Portuguesa, 32*(3), 227-235. doi:10.20344/amp.11923

Donoghue, K., Doody, G. A., Murray, R. M., Jones, P. B., Morgan, C., Dazzan, P., . . . Maccabe, J. H. (2014). Cannabis use, gender and age of onset of schizophrenia: data from the AESOP study. *Psychiatry Research, 215*(3), 528-532. doi:10.1016/j.psychres.2013.12.038

Dr Caleb Lack. (N.A.). History of the DSM. Retrieved from https://courses.lumenlearning.com/abnormalpsychology/chapter/history-of-the-dsm/. Access: 9/9/2021

Dumas, P., Saoud, M., Bouafia, S., Gutknecht, C., Ecochard, R., Dalery, J., . . . d'Amato, T. (2002). Cannabis use correlates with schizotypal personality traits in healthy students. *Psychiatry Research, 109*(1), 27-35. doi:10.1016/s0165-1781(01)00358-4

Egger, M., & Smith, G. D. (1997). Meta-analyses. Potentials and promise. *BMJ 1997, 315*(1371), 4.

ElSohly, M. A., Radwan, M. M., Gul, W., Chandra, S., & Galal, A. (2017). Phytochemistry of Cannabis sativa L. *Progress in the Chemistry of Organic Natural Products, 103*, 1-36. doi:10.1007/978-3-319-45541-9_1

Elsohly, M. A., & Slade, D. (2005). Chemical constituents of marijuana: the complex mixture of natural cannabinoids. *Life Sciences, 78*(5), 539-548. doi:10.1016/j.lfs.2005.09.011

Englund, A., Morrison, P. D., Nottage, J., Hague, D., Kane, F., Bonaccorso, S., . . . Kapur, S. (2013). Cannabidiol inhibits THC-elicited paranoid symptoms and hippocampal-dependent memory impairment. *Journal of Psychopharmacology, 27*(1), 19-27. doi:10.1177/0269881112460109

Ermis, A., Erkiran, M., Dasdemir, S., Turkcan, A. S., Ceylan, M. E., Bireller, E. S., & Cakmakoglu, B. (2015). The relationship between catechol-O-methyltransferase gene Val158Met (COMT) polymorphism and premorbid cannabis use in Turkish male patients with schizophrenia. *In Vivo, 29*(1), 129-132. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/25600541

Estrada, G., Fatjo-Vilas, M., Munoz, M. J., Pulido, G., Minano, M. J., Toledo, E., . . . Fananas, L. (2011). Cannabis use and age at onset of psychosis: further evidence of interaction with COMT Val158Met polymorphism. *Acta Psychiatrica Scandinavica, 123*(6), 485-492. doi:10.1111/j.1600-0447.2010.01665.x

European Monitoring Centre for Drugs and Drug Addiction. (2021). *European Drug Report 2021: Trends and Development.*(pp. 60). doi:10.2810/18539

Farag, S., & Kayser, O. (2017). The Cannabis Plant: Botanical Aspects. In V. R. Preedy (Ed.), *Handbook of Cannabis and Related Pathologies: Biology, Pharmacology, Diagnosis, and Treatment.* (1st ed., pp. 3-12): Academic Press. doi:10.1016/B978-0-12-800756-3.00001-6

Ferdinand, R. F., Sondeijker, F., van der Ende, J., Selten, J. P., Huizink, A., & Verhulst, F. C. (2005). Cannabis use predicts future psychotic symptoms, and vice versa. *Addiction, 100*(5), 612-618. doi:10.1111/j.1360-0443.2005.01070.x

Fergusson, D. M., Horwood, L. J., & Swain-Campbell, N. R. (2003). Cannabis dependence and psychotic symptoms in young people. *Psychological Medicine, 33*(1), 15-21. doi:10.1017/s0033291702006402

Ferretjans, R., Moreira, F. A., Teixeira, A. L., & Salgado, J. V. (2012). The endocannabinoid system and its role in schizophrenia: a systematic review of the literature. *Brazilian Journal of Psychiatry, 34 Suppl 2*, S163-177. doi:10.1016/j.rbp.2012.07.003

French, L., Gray, C., Leonard, G., Perron, M., Pike, G. B., Richer, L., . . . Paus, T. (2015). Early Cannabis Use, Polygenic Risk Score for Schizophrenia and Brain Maturation in Adolescence. *JAMA Psychiatry, 72*(10), 1002-1011. doi:10.1001/jamapsychiatry.2015.1131

Frisher, M., Crome, I., Martino, O., & Croft, P. (2009). Assessing the impact of cannabis use on trends in diagnosed schizophrenia in the United Kingdom from 1996 to 2005. *Schizophrenia Research, 113*(2-3), 123-128. doi:10.1016/j.schres.2009.05.031

Gage, S. H., Jones, H. J., Burgess, S., Bowden, J., Davey Smith, G., Zammit, S., & Munafo, M. R. (2017). Assessing causality in associations between cannabis use and schizophrenia risk: a two-sample Mendelian randomization study. *Psychological Medicine, 47*(5), 971-980. doi:10.1017/S0033291716003172

Galiegue, S., Mary, S., Marchand, J., & al., e. (1995). Expression of central and peripheral cannabinoid receptors in human immune tissues and leukocyte subpopulations. *European Journal of Biochemistry, 232*, 54-61.

Galvez-Buccollini, J. A., Proal, A. C., Tomaselli, V., Trachtenberg, M., Coconcea, C., Chun, J., . . . Delisi, L. E. (2012). Association between age at onset of psychosis and age at onset of cannabis use in non-affective psychosis. *Schizophrenia Research, 139*(1-3), 157-160. doi:10.1016/j.schres.2012.06.007

Gareeva, A. E., Sharafiev, R. R., Akhmetova, E. A., Nasibullin, T. R., Fakhurtdinova, Z. R., Yuldashev, V. L., & Asadullin, A. R. (2020). Combined Influences of Genetic Factors and Attention Deficit Hyperactivity Disorder on the Development of Dependence on Synthetic Cannabinoids. *Neuroscience and Behavioral Physiology, 50*, 1105–1111. doi:10.1007/s11055-020-01029-3

Gicas, K. M., Cheng, A., Panenka, W. J., Kim, D. D., Yau, J. C., Procyshyn, R. M., . . . Barr, A. M. (2021). Differential effects of cannabis exposure during early versus later adolescence on the expression of psychosis in homeless and precariously housed adults. *Progress in Neuro-Psychopharmacology & Biological Psychiatry, 106*, 110084. doi:10.1016/j.pnpbp.2020.110084

Giordano, G. N., Ohlsson, H., Sundquist, K., Sundquist, J., & Kendler, K. S. (2015). The association between cannabis abuse and subsequent schizophrenia: a Swedish national co-relative control study. *Psychological Medicine, 45*(2), 407-414. doi:10.1017/S0033291714001524

Giorgetti, A., Busardo, F. P., Tittarelli, R., Auwarter, V., & Giorgetti, R. (2020). Post-Mortem Toxicology: A Systematic Review of Death Cases Involving Synthetic Cannabinoid Receptor Agonists. *Frontiers in Psychiatry, 11*, 464. doi:10.3389/fpsyt.2020.00464

Glass, G. V. (1976). Primary, Secondary, and Meta-Analysis of Research. *Educational Research, 10*, 3-8.

Goldberger, C., Dervaux, A., Gourion, D., Bourdel, M. C., Loo, H., Laqueille, X., & Krebs, M. O. (2010). Variable individual sensitivity to cannabis in patients with schizophrenia. *International Journal of Neuropsychopharmacology, 13*(9), 1145-1154. doi:10.1017/S1461145710000647

Gonzalez-Pinto, A., Vega, P., Ibanez, B., Mosquera, F., Barbeito, S., Gutierrez, M., . . . Vieta, E. (2008). Impact of cannabis and other drugs on age at onset of psychosis. *Journal of Clinical Psychiatry, 69*(8), 1210-1216. doi:10.4088/jcp.v69n0802

Gouvea, E. S., Santos, A. F. F., Ota, V. K., Mrad, V., Gadelha, A., Bressan, R. A., . . . Belangero, S. I. (2017). The role of the CNR1 gene in schizophrenia: a systematic review including unpublished data. *Brazilian Journal of Psychiatry, 39*(2), 160-171. doi:10.1590/1516-4446-2016-1969

Grech, A., Van Os, J., Jones, P. B., Lewis, S. W., & Murray, R. M. (2005). Cannabis use and outcome of recent onset psychosis. *European Psychiatry, 20*(4), 349-353. doi:10.1016/j.eurpsy.2004.09.013

Guo, J., & Ikeda, S. R. (2004). Endocannabinoids modulate N-type calcium channels and G-protein-coupled inwardly rectifying potassium channels via CB1 cannabinoid receptors heterologously expressed in mammalian neurons. *Molecular Pharmacology, 65*(3), 665-674. doi:10.1124/mol.65.3.665

Gur, R. E., Turetsky, B. I., Cowell, P. E., Finkelman, C., Maany, V., Grossman, R. I., . . . Gur, R. C. (2000). Temporolimbic volume reductions in schizophrenia. *Archives of General Psychiatry, 57*(8), 769-775. doi:10.1001/archpsyc.57.8.769

Gurney, S. M., Scott, K. S., Kacinko, S. L., Presley, B. C., & Logan, B. K. (2014). Pharmacology, Toxicology, and Adverse Effects of Synthetic Cannabinoid Drugs. *Forensic Science Review, 26*(1), 53-78. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/26226970

Gutierrez, B., Rivera, M., Obel, L., McKenney, K., Martinez-Leal, R., Molina, E., . . . Cervilla, J. (2009). Variability in the COMT gene and modification of the risk of schizophrenia conferred by cannabis consumption. *Revista de Psiquiatría y Salud Mental, 2*(2), 89-94. doi:10.1016/S1888-9891(09)72250-5

Hall, W., & Solowij, N. (1998). Adverse effects of cannabis. *Lancet, 352*, 1611-1615.

Hambrecht, M., & Hafner, H. (2000). Cannabis, vulnerability, and the onset of schizophrenia: an epidemiological perspective. *Australian & New Zealand Journal of Psychiatry, 34*(3), 468-475. doi:10.1080/j.1440-1614.2000.00736.x

Hampson, A. J., Grimaldi, M., Axelrod, J., & Wink, D. (1998). Cannabidiol and (-)D9-tetrahydrocannabinol are neuroprotective antioxidants. *Proceedings of the National Academy of Sciences of the United States of America, 95*, 8268-8273.

Harvey, D. J. (N.A.). Metabolism and pharmacokinetics of the cannabinoids. *Biochemistry and Physiology of substance abuse, CRC Press*, 279-365.

Hasan, A., von Keller, R., Friemel, C. M., Hall, W., Schneider, M., Koethe, D., . . . Hoch, E. (2020). Cannabis use and psychosis: a review of reviews. *European Archives of Psychiatry and Clinical Neuroscience, 270*(4), 403-412. doi:10.1007/s00406-019-01068-z

Heinz, A., Voss, M., Lawrie, S. M., Mishara, A., Bauer, M., Gallinat, J., . . . Galderisi, S. (2016). Shall we really say goodbye to first rank symptoms? *European Psychiatry, 37*, 8-13. doi:10.1016/j.eurpsy.2016.04.010

Heishman, S. J., Stitzer, M. L., & Yingling, J. E. (1989). Effects of tetrahydrocannabinol content on marijuana smoking behavior, subjective reports, and performance. *Pharmacology Biochemistry and Behavior, 34(1)*, 173-179. doi:10.1016/0091-3057(89)90369-9

Helle, S., Ringen, P. A., Melle, I., Larsen, T. K., Gjestad, R., Johnsen, E., . . . Loberg, E. M. (2016). Cannabis use is associated with 3years earlier onset of schizophrenia spectrum disorder in a naturalistic, multi-site sample (N=1119). *Schizophrenia Research, 170*(1), 217-221. doi:10.1016/j.schres.2015.11.027

Henquet, C., Krabbendam, L., Spauwen, J., Kaplan, C., Lieb, R., Wittchen, H. U., & van Os, J. (2005). Prospective cohort study of cannabis use, predisposition for psychosis, and psychotic symptoms in young people. *BMJ, 330*(7481), 11. doi:10.1136/bmj.38267.664086.63

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. doi:10.1093/schbul/sbi027

Henquet, C., Rosa, A., Krabbendam, L., Papiol, S., Fananas, L., Drukker, M., . . . van Os, J. (2006). An experimental study of catechol-o-methyltransferase Val158Met moderation

of delta-9-tetrahydrocannabinol-induced effects on psychosis and cognition. *Neuropsychopharmacology, 31*(12), 2748-2757. doi:10.1038/sj.npp.1301197

Henry, D. J., & Chavkin, C. (1995). Activation of inwardly rectifying potassium channels (GIRK1) by co-expressed rat brain cannabinoid receptors in Xenopus oocytes. *Neuroscience Letters, 186*(2-3), 91-94. doi:10.1016/0304-3940(95)11289-9

Hickman, M., Vickerman, P., Macleod, J., Kirkbride, J., & Jones, P. B. (2007). Cannabis and schizophrenia: model projections of the impact of the rise in cannabis use on historical and future trends in schizophrenia in England and Wales. *Addiction, 102*(4), 597-606. doi:10.1111/j.1360-0443.2006.01710.x

Hiemstra, M., Nelemans, S. A., Branje, S., van Eijk, K. R., Hottenga, J. J., Vinkers, C. H., . . . Boks, M. P. (2018). Genetic vulnerability to schizophrenia is associated with cannabis use patterns during adolescence. *Drug and Alcohol Dependence, 190*, 143-150. doi:10.1016/j.drugalcdep.2018.05.024

Hill, A. B. (1965). The Environment and Disease: Association or Causation? *Proceedings of the Royal Society of Medicine, 58*, 295-300. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/14283879

Hirsch, J. A., Nicola, G., McGinty, G., Liu, R. W., Barr, R. M., Chittle, M. D., & Manchikanti, L. (2016). ICD-10: History and Context. *American Journal of Neuroradiology, 37*(4), 596-599. doi:10.3174/ajnr.A4696

Hollis, C., Groom, M. J., Das, D., Calton, T., Bates, A. T., Andrews, H. K., . . . Liddle, P. F. (2008). Different psychological effects of cannabis use in adolescents at genetic high risk for schizophrenia and with attention deficit/hyperactivity disorder (ADHD). *Schizophrenia Research, 105*(1-3), 216-223. doi:10.1016/j.schres.2008.07.010

Honorio, K. M., de Lima, E. F., Quiles, M. G., Romero, R. A., Molfetta, F. A., & da Silva, A. B. (2010). Artificial neural networks and the study of the psychoactivity of cannabinoid compounds. *Chemical Biology & Drug Design, 75*(6), 632-640. doi:10.1111/j.1747-0285.2010.00966.x

Howlett, A. C. (1998). The CB1 cannabinoid receptor in the Brain. *Neurobiology of Disease, 5*, 405-406.

Howlett, A. C., Barth, F., Bonner, T. I., Cabral, G., Casellas, P., Devane, W. A., & et al. (2002). International Union of Pharmacology. XXVII. Classification of Cannabinoid Receptors. *Pharmacological Reviews, 54*, 161-202.

Huque, M. F. (1988). Experiences with meta-analysis in NDA submissions. *Proceedings of the Biopharmaceutical Section of the American Statistical Association 1988, 2*, 28-33.

Ibeas Bih, C., Chen, T., Nunn, A. V., Bazelot, M., Dallas, M., & Whalley, B. J. (2015). Molecular Targets of Cannabidiol in Neurological Disorders. *Neurotherapeutics, 12*(4), 699-730. doi:10.1007/s13311-015-0377-3

Ilyasov, A. A., Milligan, C. E., Pharr, E. P., & Howlett, A. C. (2018). The Endocannabinoid System and Oligodendrocytes in Health and Disease. *Frontiers in Neuroscience, 12*, 733. doi:10.3389/fnins.2018.00733

Ishac, E. J., Jiang, L., Lake, K. D., Varga, K., Abood, M. E., & Kunus, G. (1996). Inhibition of exocytotic noradrenaline release by presynaptic cannabinoid CB1 receptors on peripheral sympathetic nerves. *British Journal of Pharmacology, 118*, 2023-2028.

Iversen, L. (2004). How cannabis works in the brain. In D. Castle & R. Murray (Eds.), *Marijuana and madness: Psychiatry and neurobiology* (pp. 19-40). Cambridge: Cambridge University Press.

Jablensky, A. (2010). The diagnostic concept of schizophrenia: its history, evolution, and future prospects. *Dialogues in Clinical Neuroscience, 12*(3), 271-287. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/20954425

Jain, S., & Srivastava, A. S. (2017). Frontal Lobe Abnormality And Psychosis In Traumatic Brain Injury And Cannabis Abuse. *ASEAN Journal of Psychiatry, 18*(1).

James, A., Hough, M., James, S., Winmill, L., Burge, L., Nijhawan, S., . . . Zarei, M. (2011). Greater white and grey matter changes associated with early cannabis use in adolescent-onset schizophrenia (AOS). *Schizophrenia Research, 128*(1-3), 91-97. doi:10.1016/j.schres.2011.02.014

James, A., James, C., & Thwaites, T. (2013). The brain effects of cannabis in healthy adolescents and in adolescents with schizophrenia: a systematic review. *Psychiatry Research, 214*(3), 181-189. doi:10.1016/j.pscychresns.2013.07.012

Kaló, Z., Kassai, S., Rácz, J., & Van Hout, M. C. (2018). Synthetic cannabinoids (SCs) in metaphors: A metaphorical analysis of user experiences of synthetic cannabinoids in two countries. *International Journal of Mental Health and Addiction*. doi:10.1007/s11469-018-9970-0

Katona, I., & Freund, T. F. (2008). Endocannabinoid signaling as a synaptic circuit breaker in neurological disease. *Nature Medicine, 14*(9), 923-930. doi:10.1038/nm.f.1869

Kaur, R., Ambwani, S. R., & Singh, S. (2016). Endocannabinoid System: A Multi-Facet Therapeutic Target. *Current Clinical Pharmacology, 11*(2), 110-117. doi:10.2174/1574884711666160418105339

Kendell, R., & Jablensky, A. (2003). Distinguishing between the validity and utility of psychiatric diagnoses. *American Journal of Psychiatry, 160*(1), 4-12. doi:10.1176/appi.ajp.160.1.4

Kim, E. S., & Mahlberg, P. G. (1999). Immunochemical localization of tetrahydrocannabinol (THC) in chemically fixed glandular thrichomes of Cannabis (Cannabaceae). *Korean Journal of Biological Sciences, 3:2*, 215-219. doi:10.1080/12265071.1999.9647488

Koen, L., Jonathan, R., & Niehaus, D. J. H. (2009). Cannabis use and abuse correlates in a homogeneous South African schizophrenia population. *South African Journal of Psychology, 15(1)*, 8–12. Retrieved from https://www.ajol.info/index.php/sajpsyc/article/view/50420

Koethe, D., Gerth, C. W., Neatby, M. A., Haensel, A., Thies, M., Schneider, U., . . . Leweke, F. M. (2006). Disturbances of visual information processing in early states of psychosis and experimental delta-9-tetrahydrocannabinol altered states of consciousness. *Schizophrenia Research, 88*(1-3), 142-150. doi:10.1016/j.schres.2006.07.023

Kokona, A., Tarricone, I., Di Forti, M., & Carra, E. (2017). Cannabis, Migration, and Psychosis Onset. In V. R. Preedy (Ed.), *Handbook of Cannabis and Related Pathologies: Biology, Pharmacology, Diagnosis, and Treatment* (1st ed., pp. 24-32): Academic Press. doi:10.1016/B978-0-12-800756-3.00010-7

Kristensen, K., & Cadenhead, K. S. (2007). Cannabis abuse and risk for psychosis in a prodromal sample. *Psychiatry Research, 151*(1-2), 151-154. doi:10.1016/j.psychres.2006.10.001

Krotulski, A. J., Cannaert, A., Stove, C., & Logan, B. K. (2021). The next generation of synthetic cannabinoids: Detection, activity, and potential toxicity of pent-4en and but-3en analogues including MDMB-4en-PINACA. *Drug Testing and Analysis, 13*(2), 427-438. doi:10.1002/dta.2935

Kuepper, R., van Os, J., Lieb, R., Wittchen, H. U., Hofler, M., & Henquet, C. (2011). Continued cannabis use and risk of incidence and persistence of psychotic symptoms: 10 year follow-up cohort study. *BMJ, 342*, d738. doi:10.1136/bmj.d738

Kumra, S., Robinson, P., Tambyraja, R., Jensen, D., Schimunek, C., Houri, A., . . . Lim, K. (2012). Parietal lobe volume deficits in adolescents with schizophrenia and adolescents with cannabis use disorders. *The Journal of the American Academy of Child & Adolescent Psychiatry's, 51*(2), 171-180. doi:10.1016/j.jaac.2011.11.001

Lodhi, R. J., Wang, Y., Rossolatos, D., MacIntyre, G., Bowker, A., Crocker, C., . . . Aitchison, K. J. (2017). Investigation of the COMT Val158Met variant association with age of onset of psychosis, adjusting for cannabis use. *Brain and Behavior, 7*(11), e00850. doi:10.1002/brb3.850

Lunn, C. A., Fine, J. S., Rojas-Triana, A., Jackson, J. V., Fan, X., Kung, T. T., . . . Bober, L. A. (2006). A novel cannabinoid peripheral cannabinoid receptor-selective inverse agonist blocks leukocyte recruitment in vivo. *Journal of Pharmacology and Experimental Therapeutics, 316*(2), 780-788. doi:10.1124/jpet.105.093500

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. doi:10.1016/j.neuropharm.2005.03.016

Malchow, B., Hasan, A., Schneider-Axmann, T., Jatzko, A., Gruber, O., Schmitt, A., . . . Wobrock, T. (2013). Effects of cannabis and familial loading on subcortical brain volumes in first-episode schizophrenia. *European Archives of Psychiatry and Clinical Neuroscience, 263 Suppl 2*, S155-168. doi:10.1007/s00406-013-0451-y

Maldonado, R., Banos, J. E., & Cabanero, D. (2016). The endocannabinoid system and neuropathic pain. *Pain, 157 Suppl 1*, S23-S32. doi:10.1097/j.pain.0000000000000428

Mallet, J., Ramoz, N., Le Strat, Y., Gorwood, P., & Dubertret, C. (2017). Heavy cannabis use prior psychosis in schizophrenia: clinical, cognitive and neurological evidences for a new endophenotype? *European Archives of Psychiatry and Clinical Neuroscience, 267*(7), 629-638. doi:10.1007/s00406-017-0767-0

Manrique-Garcia, E., Zammit, S., Dalman, C., Hemmingsson, T., Andreasson, S., & Allebeck, P. (2012). Cannabis, schizophrenia and other non-affective psychoses: 35 years of follow-up of a population-based cohort. *Psychological Medicine, 42*(6), 1321-1328. doi:10.1017/S0033291711002078

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. doi:10.1093/schbul/sbw003

Martin, A. K., Robinson, G., Reutens, D., & Mowry, B. (2014). Cannabis abuse and age at onset in schizophrenia patients with large, rare copy number variants. *Schizophrenia Research, 155*(1-3), 21-25. doi:10.1016/j.schres.2014.03.004

Mauri, M. C., Volonteri, L. S., De Gaspari, I. F., Colasanti, A., Brambilla, M. A., & Cerruti, L. (2006). Substance abuse in first-episode schizophrenic patients: a retrospective study. *Clinical Practice and Epidemiology in Mental Health, 2*, 4. doi:10.1186/1745-0179-2-4

McGrath, J., Welham, J., Scott, J., Varghese, D., Degenhardt, L., Hayatbakhsh, M. R., . . . Najman, J. M. (2010). Association between cannabis use and psychosis-related outcomes using sibling pair analysis in a cohort of young adults. *Archives of General Psychiatry, 67*(5), 440-447. doi:10.1001/archgenpsychiatry.2010.6

McHugh, M. J., McGorry, P. D., Yung, A. R., Lin, A., Wood, S. J., Hartmann, J. A., & Nelson, B. (2017). Cannabis-induced attenuated psychotic symptoms: implications for prognosis in young people at ultra-high risk for psychosis. *Psychological Medicine, 47*(4), 616-626. doi:10.1017/S0033291716002671

Mechoulam, R., Devane, W. A., & Glaser, R. (1992). Cannabinoid geometry and biological activity in marijuana/Cannabinoids. In Murphy L. & Bartke A. (Eds.), *Neurobiology and Neurophysiology.* (pp. 1-34). Boca Ratón, FL: CRC Press.

Mechoulam, R., & Hanuš, L. (2004). The cannabinoid system: from the point of view of a chemist. In D. Castle & R. Murray (Eds.), *Marijuana and madness: Psychiatry and neurobiology* (pp. 1-18). Cambridge: Cambridge University Press.

Meehl, P. E. (1962). Schizotaxia, schizotypy, schizophrenia. *American Psychologist, 17(12)*, 827–838. doi:10.1037/h0041029

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. doi:10.1523/JNEUROSCI.4503-03.2004

Meyer-Lindenberg, A., Nichols, T., Callicott, J. H., Ding, J., Kolachana, B., Buckholtz, J., . . . Weinberger, D. R. (2006). Impact of complex genetic variation in COMT on human brain function. *Molecular Psychiatry, 11*(9), 867-877, 797. doi:10.1038/sj.mp.4001860

Micale, V., & Drago, F. (2018). Endocannabinoid system, stress and HPA axis. *European Journal of Pharmacology, 834*, 230-239. doi:10.1016/j.ejphar.2018.07.039

Miettunen, J., Tormanen, S., Murray, G. K., Jones, P. B., Maki, P., Ebeling, H., . . . Veijola, J. (2008). Association of cannabis use with prodromal symptoms of psychosis in adolescence. *The British Journal of Psychiatry, 192*(6), 470-471. doi:10.1192/bjp.bp.107.045740

Mills, B., Yepes, A., & Nugent, K. (2015). Synthetic Cannabinoids. *The American Journal of the Medical Sciences, 350*(1), 59-62. doi:10.1097/MAJ.0000000000000466

Moeller, S., Lucke, C., Struffert, T., Schwarze, B., Gerner, S. T., Schwab, S., . . . Muller, H. H. (2017). Ischemic stroke associated with the use of a synthetic cannabinoid (spice). *Asian Journal of Psychiatry, 25*, 127-130. doi:10.1016/j.ajp.2016.10.019

Molina-Holgado, E., Vela, J. M., Arevalo-Martin, A., Almazan, G., Molina-Holgado, F., Borrell, J., & Guaza, C. (2002). Cannabinoids promote oligodendrocyte progenitor survival: involvement of cannabinoid receptors and phosphatidylinositol-3 kinase/Akt

signaling. *Journal of Neuroscience, 22*(22), 9742-9753. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/12427829

Molnar, G., Feeney, M. G., & Fava, G. A. (1988). Duration and symptoms of bipolar prodromes. *American Journal of Psychiatry, 145*(12), 1576-1578. doi:10.1176/ajp.145.12.1576

Monteleone, P., Di Filippo, C., Fabrazzo, M., Milano, W., Martiadis, V., Corrivetti, G., . . . Maj, M. (2014). Flattened cortisol awakening response in chronic patients with schizophrenia onset after cannabis exposure. *Psychiatry Research, 215*(2), 263-267. doi:10.1016/j.psychres.2013.12.016

Moore, T. H., Zammit, S., Lingford-Hughes, A., Barnes, T. R., Jones, P. B., Burke, M., & Lewis, G. (2007). Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review. *Lancet, 370*(9584), 319-328. doi:10.1016/S0140-6736(07)61162-3

Morales, P., Hurst, D. P., & Reggio, P. H. (2017). Molecular Targets of the Phytocannabinoids: A Complex Picture. *Progress in the Chemistry of Organic Natural Products, 103*, 103-131. doi:10.1007/978-3-319-45541-9_4

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. doi:10.1192/bjp.bp.107.046649

Morrison, P. D., & Murray, R. M. (2009). From real-world events to psychosis: the emerging neuropharmacology of delusions. *Schizophrenia Bulletin, 35*(4), 668-674. doi:10.1093/schbul/sbp049

Mortimer, A. M. (2011). The Magic Shotgun: Does It Fit the Clinician and Will It Point at Schizophrenia? In Ritsner M. S. (Ed.), *Handbook of Schizophrenia Spectrum Disorders, Volume III: Therapeutic Approaches, Comorbidity, and Outcomes.* (Vol. III, pp. 23-49): Springer Science+Business Media B.V. doi:10.1007/978-94-007-0834-1_2

Muller, H. H., Kornhuber, J., & Sperling, W. (2016). The behavioral profile of spice and synthetic cannabinoids in humans. *Brain Research Bulletin, 126*(Pt 1), 3-7. doi:10.1016/j.brainresbull.2015.10.013

Murray, R. M., Morrison, P. D., Henquet, C., & Di Forti, M. (2007). Cannabis, the mind and society: the hash realities. *Nature Reviews Neuroscience, 8*(11), 885-895. doi:10.1038/nrn2253

Myles, N., Newall, H., Nielssen, O., & Large, M. (2012). The Association between Cannabis Use and Earlier Age at Onset of Schizophrenia and other Psychoses: Meta-analysis of Possible Confounding Factors. *Current Pharmaceutical Design, 18*, 5055-5069.

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

National Center for Biotechnology Information. (2021). PubChem Compound Summary for CID 5282280, 2-Arachidonoylglycerol. Retrieved from https://pubchem.ncbi.nlm.nih.gov/compound/2-Arachidonoylglycerol. Access: 4/9/2021

Netzahualcoyotzi-Piedra, C., Muñoz-Arenas, G., Martínez-García, I., Florán-Garduño, B., & Limón-Pérez de León, I. D. (2009). La marihuana y el sistema endocanabinoide: De sus

efectos recreativos a la terapêutica. *Revista Biomédica 2009, 20*, 128-153. Retrieved from https://www.medigraphic.com/pdfs/revbio/bio-2009/bio092f.pdf

Nielsen, J. (2011). Schizophrenia and Medical Illness: Is Medical Illness the Consequence of Schizophrenia or Its Treatment? In Ritsner M. S. (Ed.), *Handbook of Schizophrenia Spectrum Disorders, Volume III: Therapeutic Approaches, Comorbidity, and Outcomes.* (Vol. III, pp. 267-287): Springer Science+Business Media B.V. doi:10.1007/978-94-007-0834-1_13

Nielsen, S. M., Toftdahl, N. G., Nordentoft, M., & Hjorthoj, C. (2017). Association between alcohol, cannabis, and other illicit substance abuse and risk of developing schizophrenia: a nationwide population based register study. *Psychological Medicine, 47*(9), 1668-1677. doi:10.1017/S0033291717000162

Norrod, A. G., & Puffenbarger, R. A. (2007). Genetic polymorphisms of the endocannabinoid system. *Chemistry & Biodiversity, 4*(8), 1926-1932. doi:10.1002/cbdv.200790160

Núñez, E., Benito, C., Tolón, R. M., Hillard, C. J., Griffin, W. S. T., & Romero, J. (2008). Glial expression of cannabinoid CB2 receptors and fatty acid amide hydrolase are beta amyloid-linked events in Down's syndrome. *Neuroscience, 151*, 104-110.

Nunn, J. A., Rizza, F., & Peters, E. R. (2001). The incidence of schizotypy among cannabis and alcohol users. *The Journal of Nervous and Mental Disease, 189*(11), 741-748. doi:10.1097/00005053-200111000-00002

Nurmedov, S., Metin, B., Ekmen, S., Noyan, O., Yilmaz, O., Darcin, A., & Dilbaz, N. (2015). Thalamic and Cerebellar Gray Matter Volume Reduction in Synthetic Cannabinoids Users. *European Addiction Research, 21*(6), 315-320. doi:10.1159/000430437

O'Connor, K., & Lecomte, T. (2011). An Overview of Cognitive Behaviour Therapy in Schizophrenia Spectrum Disorders. In Ritsner M.S. (Ed.), *Handbook of Schizophrenia Spectrum Disorders, Volume III: Therapeutic Approaches, Comorbidity, and Outcomes.* (Vol. III, pp. 245-265): Springer Science+Business Media B.V. doi:10.1007/978-94-007-0834-1_12

Pasman, J. A., Verweij, K. J. H., Gerring, Z., Stringer, S., Sanchez-Roige, S., Treur, J. L., . . . Vink, J. M. (2018). GWAS of lifetime cannabis use reveals new risk loci, genetic overlap with psychiatric traits, and a causal influence of schizophrenia. *Nature Neuroscience, 21*(9), 1161-1170. doi:10.1038/s41593-018-0206-1

Patel, S., Khan, S., M, S., & Hamid, P. (2020). The Association Between Cannabis Use and Schizophrenia: Causative or Curative? A Systematic Review. *Cureus, 12*(7), e9309. doi:10.7759/cureus.9309

Pazos, M. R., Nuñez, E., Benito, C., Tolón, R. M., & Romero, J. (2005). Functional neuroanatomy of the endocannabinoid system. *Pharmacology Biochemistry and Behavior, 81:239-47*.

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). doi:10.3390/ijerph16214149

Pelayo-Teran, J. M., Perez-Iglesias, R., Mata, I., Carrasco-Marin, E., Vazquez-Barquero, J. L., & Crespo-Facorro, B. (2010). Catechol-O-Methyltransferase (COMT) Val158Met variations and cannabis use in first-episode non-affective psychosis: clinical-onset implications. *Psychiatry Research, 179*(3), 291-296. doi:10.1016/j.psychres.2009.08.022

Pertwee, R. G. (1997). Pharmacology of cannabinoid CB1 and CB2 receptors. *Pharmacology & Therapeutics, 74*(2), 129-180. doi:10.1016/s0163-7258(97)82001-3

Pertwee, R. G. (2008). The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: delta9-tetrahydrocannabinol, cannabidiol and delta9-tetrahydrocannabivarin. *British Journal of Pharmacology, 153*(2), 199-215. doi:10.1038/sj.bjp.0707442

Pertwee, R. G., Howlett, A. C., Abood, M. E., Alexander, S. P., Di Marzo, V., Elphick, M. R., . . . Ross, R. A. (2010). International Union of Basic and Clinical Pharmacology. LXXIX. Cannabinoid receptors and their ligands: beyond CB(1) and CB(2). *Pharmacological Reviews, 62*(4), 588-631. doi:10.1124/pr.110.003004

Peters, B. D., de Haan, L., Vlieger, E. J., Majoie, C. B., den Heeten, G. J., & Linszen, D. H. (2009). Recent-onset schizophrenia and adolescent cannabis use: MRI evidence for structural hyperconnectivity? *Psychopharmacology Bulletin, 42*(2), 75-88. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/19629024

Piomelli, D. (2003). The molecular logic of endocannabinoid signalling. *Nature Reviews Neuroscience, 4*(11), 873-884. doi:10.1038/nrn1247

Piomelli, D., Giuffrida, A., Calignano, A., & Rodriguez de Fonseca, F. (2000). The endocannabinoid system as a target for therapeutic drugs. *Trends in Pharmacological Sciences, 21*(6), 218-224. doi:10.1016/s0165-6147(00)01482-6

Pisanti, S., Malfitano, A. M., Ciaglia, E., Lamberti, A., Ranieri, R., Cuomo, G., . . . Bifulco, M. (2017). Cannabidiol: State of the art and new challenges for therapeutic applications. *Pharmacology & Therapeutics, 175*, 133-150. doi:10.1016/j.pharmthera.2017.02.041

Potter, D. J., Clark, P., & Brown, M. B. (2008). Potency of delta 9-THC and other cannabinoids in cannabis in England in 2005: implications for psychoactivity and pharmacology. *Journal of Forensic Sciences, 53*(1), 90-94. doi:10.1111/j.1556-4029.2007.00603.x

Potts, A. J., Cano, C., Thomas, S. H. L., & Hill, S. L. (2020). Synthetic cannabinoid receptor agonists: classification and nomenclature. *Clinical Toxicology (Philadelphia), 58*(2), 82-98. doi:10.1080/15563650.2019.1661425

Power, R. A., Verweij, K. J., Zuhair, M., Montgomery, G. W., Henders, A. K., Heath, A. C., . . . Martin, N. G. (2014). Genetic predisposition to schizophrenia associated with increased use of cannabis. *Molecular Psychiatry, 19*(11), 1201-1204. doi:10.1038/mp.2014.51

Prandi, C., Blangetti, M., Namdar, D., & Koltai, H. (2018). Structure-Activity Relationship of Cannabis Derived Compounds for the Treatment of Neuronal Activity-Related Diseases. *Molecules, 23*(7). doi:10.3390/molecules23071526

Radhakrishnan, R., Wilkinson, S. T., & D'Souza, D. C. (2014). Gone to Pot - A Review of the Association between Cannabis and Psychosis. *Frontiers in Psychiatry, 5*, 54. doi:10.3389/fpsyt.2014.00054

Rado, S. (1960). Theory and therapy: the theory of schizotypal organization and its application to the treatment of decompensated schizotypal behaviour. In Scher S. C. & Davis H. R. (Eds.), *The Outpatient Treatment of Schizophrenia.* New York, NY: Grune and Stratton.

Ramsay, C. E., & Compton, M. T. (2011). The Interface of Cannabis Misuse and Schizophrenia-Spectrum Disorders. In M. Ritsner (Ed.), *Handbook of Schizophrenia Spectrum Disorders* (Vol. III): Springer, Dordrecht. doi:10.1007/978-94-007-0834-1_14

Realini, N., Rubino, T., & Parolaro, D. (2009). Neurobiological alterations at adult age triggered by adolescent exposure to cannabinoids. *Pharmacological Research, 60*(2), 132-138. doi:10.1016/j.phrs.2009.03.006

Ritsner, M. S., & Lerner, V. (2011). Advancing Neuroprotective-Based Treatments for Schizophrenia. In Ritsner M. S. (Ed.), *Handbook of Schizophrenia Spectrum Disorders, Volume III: Therapeutic Approaches, Comorbidity, and Outcomes.* (Vol. III, pp. 51-80): Springer Science+Business Media, B.V. doi:10.1007/978-94-007-0834-1_3

Rodrigo, C., Welgama, S., Gunawardana, A., Maithripala, C., Jayananda, G., & Rajapakse, S. (2010). A retrospective analysis of cannabis use in a cohort of mentally ill patients in Sri Lanka and its implications on policy development. *Substance Abuse Treatment, Prevention, and Policy, 5*, 16. doi:10.1186/1747-597X-5-16

Rodrigues, V. (2012). *Métodos de avaliação da frequência de eventos adversos em contexto hospitalar: contributos de uma revisão sistemática.* (Master Thesis in Patient Safety). Universidade Nova de Lisboa, Lisboa, Escola Nacional de Saúde Pública. Retrieved from https://run.unl.pt/handle/10362/9578

Roos, J. L., Pretorius, H. W., Karayiorgou, M., & Boraine, H. (2006). Cannabis and other variables affecting age at onset in a schizophrenia founder population. *South African Psychiatry Review, 9*, 99-103. doi:10.4314/ajpsy.v9i2.30212

Roser, P., Vollenweider, F. X., & Kawohl, W. (2010). Potential antipsychotic properties of central cannabinoid (CB1) receptor antagonists. *The World Journal of Biological Psychiatry, 11*(2 Pt 2), 208-219. doi:10.3109/15622970801908047

Sarrazin, S., Louppe, F., Doukhan, R., & Schurhoff, F. (2015). A clinical comparison of schizophrenia with and without pre-onset cannabis use disorder: a retrospective cohort study using categorical and dimensional approaches. *Annals of General Psychiatry, 14*, 44. doi:10.1186/s12991-015-0083-x

Scherma, M., Masia, P., Satta, V., Fratta, W., Fadda, P., & Tanda, G. (2019). Brain activity of anandamide: a rewarding bliss? *Acta Pharmacologica Sinica, 40*(3), 309-323. doi:10.1038/s41401-018-0075-x

Schiffman, J., Nakamura, B., Earleywine, M., & LaBrie, J. (2005). Symptoms of schizotypy precede cannabis use. *Psychiatry Research, 134*(1), 37-42. doi:10.1016/j.psychres.2005.01.004

Schizophrenia Working Group of the Psychiatric Genomics, C. (2014). Biological insights from 108 schizophrenia-associated genetic loci. *Nature, 511*(7510), 421-427. doi:10.1038/nature13595

Schlatter, J., & Atta, U.-R. (2014). Chapter 9 - Synthetic Cannabinoids: Synthesis and Biological Activities. In Atta U-R. (Ed.), *Studies in Natural Products Chemistry* (Vol. 43, pp. 291-311). Amsterdam, Netherlands: Elsevier.

Schneider, M., Schomig, E., & Leweke, F. M. (2008). Acute and chronic cannabinoid treatment differentially affects recognition memory and social behavior in pubertal and adult rats. *Addiction Biology, 13*(3-4), 345-357. doi:10.1111/j.1369-1600.2008.00117.x

Scuderi, C., Filippis, D. D., Iuvone, T., Blasio, A., Steardo, A., & Esposito, G. (2009). Cannabidiol in medicine: a review of its therapeutic potential in CNS disorders. *Phytotherapy Research, 23*(5), 597-602. doi:10.1002/ptr.2625

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 & Biological Psychiatry, 39*(2), 234-243. doi:10.1016/j.pnpbp.2012.04.017

Semple, D. M., McIntosh, A. M., & Lawrie, S. M. (2005). Cannabis as a risk factor for psychosis: systematic review. *Journal of Psychopharmacology, 19*(2), 187-194. doi:10.1177/0269881105049040

Sevy, S., Robinson, D. G., Napolitano, B., Patel, R. C., Gunduz-Bruce, H., Miller, R., . . . Kane, J. (2010). Are cannabis use disorders associated with an earlier age at onset of psychosis? A study in first episode schizophrenia. *Schizophrenia Research, 120*(1-3), 101-107. doi:10.1016/j.schres.2010.03.037

Sewell, R. A., Ranganathan, M., & D'Souza, D. C. (2009). Cannabinoids and psychosis. *International Review of Psychiatry, 21*(2), 152-162. doi:10.1080/09540260902782802

Shahzade, C., Chun, J., DeLisi, L. E., & Manschreck, T. C. (2018). Patterns in adolescent cannabis use predict the onset and symptom structure of schizophrenia-spectrum disorder. *Schizophrenia Research, 197*, 539-543. doi:10.1016/j.schres.2018.01.008

Sharkey, K. A., & Wiley, J. W. (2016). The Role of the Endocannabinoid System in the Brain-Gut Axis. *Gastroenterology, 151*(2), 252-266. doi:10.1053/j.gastro.2016.04.015

Shenton, M. E., Kikinis, R., Jolesz, F. A., Pollak, S. D., LeMay, M., Wible, C. G., . . . et al. (1992). Abnormalities of the left temporal lobe and thought disorder in schizophrenia. A quantitative magnetic resonance imaging study. *The New England Journal of Medicine, 327*(9), 604-612. doi:10.1056/NEJM199208273270905

Smit, F., Bolier, L., & Cuijpers, P. (2004). Cannabis use and the risk of later schizophrenia: a review. *Addiction, 99*(4), 425-430. doi:10.1111/j.1360-0443.2004.00683.x

Soares-Weiser, K., Maayan, N., Bergman, H., Davenport, C., Kirkham, A. J., Grabowski, S., & Adams, C. E. (2015). First rank symptoms for schizophrenia. *Cochrane Database of Systematic Reviews, 1*, CD010653. doi:10.1002/14651858.CD010653.pub2

Spaderna, M., Addy, P. H., & D'Souza, D. C. (2013). Spicing things up: synthetic cannabinoids. *Psychopharmacology (Berl), 228*(4), 525-540. doi:10.1007/s00213-013-3188-4

Stefanis, N. C., Dragovic, M., Power, B. D., Jablensky, A., Castle, D., & Morgan, V. A. (2013). Age at initiation of cannabis use predicts age at onset of psychosis: the 7- to 8-year trend. *Schizophrenia Bulletin, 39*(2), 251-254. doi:10.1093/schbul/sbs188

Sugranyes, G., Flamarique, I., Parellada, E., Baeza, I., Goti, J., Fernandez-Egea, E., & Bernardo, M. (2009). Cannabis use and age of diagnosis of schizophrenia. *European Psychiatry, 24*(5), 282-286. doi:10.1016/j.eurpsy.2009.01.002

Susser, M. (1991). What is a cause and how do we know one? A grammar for pragmatic epidemiology. *American Journal of Epidemiology, 133*(7), 635-648. doi:10.1093/oxfordjournals.aje.a115939

Svíženská, I., Dubový, P., & Šulcová, A. (2008). Cannabinoid receptors 1 and 2 (CB1 and CB2), their distribution, ligands and functional involvement in nervous system structures-A short review. *Pharmacology Biochemistry and Behavior, 90*, 501-511.

Tamba, B. I., Stanciu, G. D., Uritu, C. M., Rezus, E., Stefanescu, R., Mihai, C. T., . . . Alexa-Stratulat, T. (2020). Challenges and Opportunities in Preclinical Research of Synthetic Cannabinoids for Pain Therapy. *Medicina (Kaunas), 56*(1). doi:10.3390/medicina56010024

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. doi:10.1016/j.schres.2013.05.028

Theunissen, E. L., Reckweg, J. T., Hutten, N., Kuypers, K. P. C., Toennes, S. W., Neukamm, M. A., . . . Ramaekers, J. G. (2021). Psychotomimetic symptoms after a moderate dose of a synthetic cannabinoid (JWH-018): implications for psychosis. *Psychopharmacology (Berl)*. doi:10.1007/s00213-021-05768-0

Uliana, V., Tomassini, A., Pollice, R., Gennarelli, M., Faravelli, F., Casacchia, M., & Di Maria, E. (2013). Cannabis and Psychosis: A Systematic Review of Genetic Studies. *Current Psychiatry Reviews, 9*, 1-15.

van Bakel, H., Stout, J. M., Cote, A. G., Tallon, C. M., Sharpe, A. G., Hughes, T. R., & Page, J. E. (2011). The draft genome and transcriptome of Cannabis sativa. *Genome Biology, 12*(10), R102. doi:10.1186/gb-2011-12-10-r102

van der Steur, S. J., Batalla, A., & Bossong, M. G. (2020). Factors Moderating the Association Between Cannabis Use and Psychosis Risk: A Systematic Review. *Brain Sciences, 10*(2). doi:10.3390/brainsci10020097

Van Mastrigt, S., Addington, J., & Addington, D. (2004). Substance misuse at presentation to an early psychosis program. *Social Psychiatry and Psychiatric Epidemiology, 39*(1), 69-72. doi:10.1007/s00127-004-0713-0

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. doi:10.1093/aje/kwf043

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. doi:10.1093/schbul/sbn117

van Winkel, R., van Beveren, N. J., Simons, C., & Genetic Risk and Outcome of Psychosis (GROUP) Investigators. (2011). AKT1 moderation of cannabis-induced cognitive alterations in psychotic disorder. *Neuropsychopharmacology, 36*(12), 2529-2537. doi:10.1038/npp.2011.141

Vaucher, J., Keating, B. J., Lasserre, A. M., Gan, W., Lyall, D. M., Ward, J., . . . Holmes, M. V. (2018). Cannabis use and risk of schizophrenia: a Mendelian randomization study. *Molecular Psychiatry, 23*(5), 1287-1292. doi:10.1038/mp.2016.252

Veen, N. D., Selten, J. P., van der Tweel, I., Feller, W. G., Hoek, H. W., & Kahn, R. S. (2004). Cannabis use and age at onset of schizophrenia. *American Journal of Psychiatry, 161*(3), 501-506. doi:10.1176/appi.ajp.161.3.501

Vemuri, V. K., & Makriyannis, A. (2015). Medicinal chemistry of cannabinoids. *Clinical Pharmacology & Therapeutics, 97*(6), 553-558. doi:10.1002/cpt.115

Veress, G., Meszar, Z., Muszil, D., Avelino, A., Matesz, K., Mackie, K., & Nagy, I. (2013). Characterisation of cannabinoid 1 receptor expression in the perikarya, and peripheral and spinal processes of primary sensory neurons. *Brain Structure and Function, 218*(3), 733-750. doi:10.1007/s00429-012-0425-2

Vindenes, V., & Mørland, J. (2017). Increasing Plant Concentrations of THC and Implications on Health Related Disorders. In V. R. Preedy (Ed.), *Handbook of Cannabis and Related Pathologies: Biology, Pharmacology, Diagnosis, and Treatment* (1st ed., pp. 24-32): Academic Press. doi:10.1016/B978-0-12-800756-3.00004-1

Wade, D., Harrigan, S., Edwards, J., Burgess, P. M., Whelan, G., & McGorry, P. D. (2006). Substance misuse in first-episode psychosis: 15-month prospective follow-up study. *The British Journal of Psychiatry, 189*, 229-234. doi:10.1192/bjp.bp.105.017236

Weiser, M., Knobler, H. Y., Noy, S., & Kaplan, Z. (2002). Clinical characteristics of adolescents later hospitalized for schizophrenia. *American Journal of Medical Genetics, 114*(8), 949-955. doi:10.1002/ajmg.10647

Welch, K. A., Moorhead, T. W., McIntosh, A. M., Owens, D. G., Johnstone, E. C., & Lawrie, S. M. (2013). Tensor-based morphometry of cannabis use on brain structure in individuals at elevated genetic risk of schizophrenia. *Psychological Medicine, 43*(10), 2087-2096. doi:10.1017/S0033291712002668

Welch, K. A., Stanfield, A. C., McIntosh, A. M., Whalley, H. C., Job, D. E., Moorhead, T. W., . . . Johnstone, E. C. (2011). Impact of cannabis use on thalamic volume in people at familial high risk of schizophrenia. *The British Journal of Psychiatry, 199*(5), 386-390. doi:10.1192/bjp.bp.110.090175

Wilson, R. I., & Nicoll, R. A. (2002). Endocannabinoid signaling in the brain. *Science, 296*(5568), 678-682. doi:10.1126/science.1063545

Wobrock, T., Czesnik, D., & Malchow, B. (2011). Schizophrenia and Comorbid Substance Abuse – Pathophysiological and Therapeutic Approaches. In Ritsner M. (Ed.), *Handbook of Schizophrenia Spectrum Disorders* (Vol. III). Dordrecht: Springer. doi:10.1007/978-94-007-0834-1_15

World Drug Report. (2021a). Booklet 2: Global Overview of Drug demand and Drug supply. In (pp. 92). Retrieved from https://www.unodc.org/res/wdr2021/field/WDR21_Booklet_2.pdf

World Drug Report. (2021b). Booklet 3: Drug market trends: Cannabis and Opioids. In (pp. 127). Retrieved from https://www.unodc.org/res/wdr2021/field/WDR21_Booklet_3.pdf

World Health Organization. (1992). *The ICD-10 Classification of Mental and Behavioral Disorders. Clinical descriptions and diagnostic guidelines.* Retrieved from https://icd.who.int/browse10/2019/en

World Health Organization. (2019). Schizophrenia. Retrieved from https://www.who.int/news-room/fact-sheets/detail/schizophrenia. Access: 10/9/2021

World Health Organization. (2021). History of ICD. Retrieved from https://www.who.int/standards/classifications/classification-of-diseases. Access: 08/20/2021

Zammit, S., Allebeck, P., Andreasson, S., Lundberg, I., & Lewis, G. (2002). Self reported cannabis use as a risk factor for schizophrenia in Swedish conscripts of 1969: historical cohort study. *BMJ, 325*(7374), 1199. doi:10.1136/bmj.325.7374.1199

Zammit, S., Spurlock, G., Williams, H., Norton, N., Williams, N., O'Donovan, M. C., & Owen, M. J. (2007). Genotype effects of CHRNA7, CNR1 and COMT in schizophrenia: interactions with tobacco and cannabis use. *The British Journal of Psychiatry, 191*, 402-407. doi:10.1192/bjp.bp.107.036129

Zou, S., & Kumar, U. (2018). Cannabinoid Receptors and the Endocannabinoid System: Signaling and Function in the Central Nervous System. *International Journal of Molecular Sciences, 19*(3). doi:10.3390/ijms19030833

Zuurman, H. H. (2008). *Clinical pharmacology of cannabinoids in early phase drug development.* (Degree of Doctor). Leiden University, The Netherlands. Retrieved from https://chdr.nl/library/clinical-pharmacology-of-cannabinoids-in-early-phase-drug-development/download