Psychiatria Danubina, 2021; Vol. 33, Suppl. 4 (part III), pp 1184-1195 *Conference paper*
Review

POSSIBLE CONSEQUENCES OF CANNABIS LEGALIZATION - WHAT DO RESEARCH SHOW?

Nera Žigić[1,2], Mevludin Hasanović[1,2], Izet Pajević[1,2] & Miro Jakovljević[3]

[1]*Department of Psychiatry University Clinical Center Tuzla, Tuzla, Bosnia and Herzegovina*
[2]*Faculty of Medicine, University of Tuzla, Tuzla, Bosnia and Herzegovina*
[3]*Department of Psychiatry and Psychological Medicine, University Hospital Centre Zagreb, Zagreb, Croatia*

SUMMARY

Background: *Indian hemp (lat. Cannabis sativa subs. Indica) has been used as a source of industrial fiber, seed oil, food, medicine for some somatic diseases, and it is also used as a psychoactive substance. Cannabis can be used by smoking, evaporation, as a food ingredient, or as an extract. Acute and chronic cannabis use has been shown to be detrimental to several aspects of psychological and physical health and many experimental studies done on healthy people indicate the potential of Δ9- tetra hydro cannabinoid (THC) in inducing transient, dose-dependent psychotic symptoms, but also affective, behavioral, cognitive, neurovegetative, and psychophysical symptoms. Cannabis is the most commonly used illegal drug globally.*

In many communities, cannabis is perceived as a low-risk drug, leading to political lobbying to decriminalize its use. The wave of laws and initiatives to liberalize cannabis use continues to spread across the United States and the rest of the world, and there seems to be a political debate in the background about the potential risks and benefits of cannabis use.

Aim is to present the possible consequences that the legalization of cannabis would have from the aspect of mental health and mental disorders.

Methods: *Authors reviewed the literature using PubMed resources on the effects of cannabis using the keywords: cannabis use, cannabis use and psychoticism, cannabis use and depression, cannabis use and anxiety, cannabis use and cognition, cannabis use and insomnia, legalization of cannabis.*

Results: *Authors examined the effects of cannabis use on psychiatric disorders and the review of the legal status of cannabis use in the world was also made. The possible consequences of cannabis legalization on the public health system were also considered, based on experiences from countries where legalization has already been done. The evidence cited in this article suggests that strong claims about the need to legalize cannabis are still questionable, and may, even in the long run, remain mixed, inconclusive, or even contradictory. Political interference in this issue can trigger a wide range of unintended but profound and lasting consequences for the health system and the health of the individual.*

Conclusion: *We recommend further research on this topic and data collection with an emphasis on the effects and consequences of cannabis use on mental health, and in particular the benefits and harmful effects of medical cannabis use.*

Key words: *legalization of cannabis - possible consequences - research*

* * * * *

INTRODUCTION

Indian hemp (lat. Cannabis sativa subs. Indica) is a subspecies of the hemp plant (lat. Cannabis sativa). It originates from the Asian continent, and due to its wide use has a cosmopolitan distribution. It has been cultivated since ancient times and has been used as a source of industrial fiber, seed oil, food, and medicine. It is also used as a psychoactive substance because it contains over 480 known active substances, of which 65 are cannabinoids. Cannabinoids have different physiological effects through interaction with specific cannabinoid receptors (CB receptors) present in the brain and on the periphery of the human body (Munro et al. 1993). CB1 receptors in the brain are particularly concentrated in anatomical regions associated with cognition, affectivity, pain perception, motor coordination, and endocrine function (Adams & Martin 1996, Herkenham et al. 1990). CB2 receptors are localized in the spleen and other peripheral tissues and may play a role in the immune-suppressive action of cannabinoids (Gardner & Lowinson 1991). Psychoactive effects arise by binding Δ9-THC (tetra hydro cannabinoid) to cannabinoid 1 (CB1) receptors (Parsons & Hurd 2015).

Cannabis can be used by smoking, evaporation, as a food ingredient, or as an extract. During smoking, cannabis produces more than 2,000 compounds that are represented by different classes of chemicals, including nitrogen compounds, amino acids, hydrocarbons, sugars, terpenes, and simple fatty acids. Overall, these compounds contribute to the unique pharmacological and toxicological properties of cannabis (Appendino et al. 2008, Pajević et al. 2021). The main psychoactive substance that contributes to the behavioral toxicity of cannabis is delta 9-tetrahydrocannabinol (Δ9-THC). The amount of THC found in cannabis has been steadily rising in the last few decades (Mehmedić et al. 2010).

Acute and chronic cannabis use has been shown to be detrimental to several aspects of psychological and physical health (Ford et al. 2017). Many experimental studies done on healthy people indicate the potential of Δ9-THC in inducing transient, dose-dependent psychotic symptoms, but also affective, behavioral, cognitive, neurovegetative, and psychophysical symptoms (Oladni & Gracini 2018).

Cannabis is the most commonly used illegal drug globally. In 2017, it is estimated that it will be used by 188 million adults (range 164-219 million) worldwide or 3.8% of the global adult population (United Nations Office on Drugs and Crime 2019). Cannabis use is more common in North America and high-income countries in Europe and Oceania (Peacock et al. 2017). Its use has increased in some low- and middle-income countries but remains low in Asia (United Nations Office on Drugs and Crime 2019).

Cannabidiol (CBD) is a major non-psychomimetic compound derived from the cannabis plant. It is thought to have therapeutic potential in a wide range of neuropsychiatric disorders (Elsaid et al. 2019).

In many communities, cannabis is perceived as a low-risk drug, leading to political lobbying to decriminalize its use. The wave of laws and initiatives to liberalize cannabis use continues to spread across the United States and the rest of the world, and there seems to be a political debate in the background about the potential risks and benefits of cannabis use.

This paper aims to present the possible consequences that the legalization of cannabis would have from the aspect of mental health and mental disorders.

We reviewed the literature using PubMed resources with the aim of summarizing existing publications with scientifically based evidence on the effects of cannabis using the keywords: cannabis use, cannabis use and psychoticism, cannabis use and depression, cannabis use and anxiety, cannabis use and cognition, cannabis use and insomnia, legalization of cannabis.

WHAT EFFECTS OF CANNABIS USE HAVE ON MENTAL HEALTH?

Can prenatal exposure to cannabis have consequences for the child?

A cross-sectional study involving 11,489 children (of whom 655 were prenatally exposed to cannabis) found that prenatal exposure to cannabis after maternal knowledge of pregnancy was associated with a higher risk of developing psychopathology during childhood, even after potentially confusing variables were considered.

The study showed that exposure to cannabis only before (413 [3.6%]) and after (242 [2.1%]) maternal knowledge of pregnancy was associated with higher psychopathological characteristics of the offspring (ie subclinical psychotic experiences and internalization, externalization, attention disorders, opinions and social problems), sleep problems and body mass index, as well as cognitive impairment and decreased gray matter volume, compared to non - exposure to cannabis in pregnancy. Post-exposure exposure alone was associated with lower birth weight as well as total intracranial volume and white matter volumes relative to pre-exposure exposure and exposure. When potentially confusing variables were included, exposure after maternal knowledge of pregnancy remained associated with an increased risk of subclinical psychotic experiences and outsourcing, attention deficit disorder, thinking, and social issues.

In light of the growing use of cannabis among pregnant women, the U.S. General Surgeon recently issued advice on cannabis use during pregnancy (Paul et al. 2020).

Cannabis use and psychoticism

There is growing evidence to support the hypothesis that cannabis consumption is a risk factor for developing psychotic symptoms. Summarizing the epidemiological evidence obtained from cross-sectional and long-term prospective studies, the important role of cannabis use in initiating and persisting psychotic disorders has been established. There is a well-founded view that the risk of developing psychoticism increases with increasing use and especially early use of cannabis, as well as the use of highly potent varieties and synthetic cannabinoids. The pathogenic mechanisms of psychotic development are focused on the effect of tetrahydrocannabinol in interaction with genetic predisposition and other environmental factors (Sideli et al. 2019). But controversy about the causal nature of this association remains (Ben Amar & Potwin 2007) and is becoming one of the leading hypotheses related to further research on the potentially harmful uses of cannabis.

Cannabis use in healthy people can lead to the development of psychotic symptoms similar to those in schizophrenia (D'Souza et al. 2004), while in patients with already developed psychotic disorders it can lead to worsening of productive psychotic symptoms (D'Souza et al. 2005). Cannabis use during the early stage of psychoticism has also been associated with an increase and severity of psychotic symptoms (Seddon et al. 2016), as it is proved by a cohort study conducted in the UK on 1,027 patients as part of the first psychotic episode. In adolescence, cannabis use is particularly dangerous because it is associated with an increased risk of developing psychiatric and addiction diseases in young adulthood (Arseneault et al. 2002, 2004, Zammit et al. 2002, Caspi et al. 2005, Moore et al. 2007). In particular, there is concern that cannabis use during adolescence results in an increased risk of developing the schizophrenic spectrum disorder (Sewell et al. 2009).

Evidence from research suggests there is a link between a dose-dependent relationship between cannabis use and the risk of developing psychoticism. They indicate that there is an increased risk of developing psychoticism, not only in terms of frequent cannabis use but also due to the use of highly potent cannabis varieties, with high concentrations of Δ9-tetrahydrocannabinol (Δ9-THC). This finding is consistent with evidence that the use of Δ9-THC can induce transient symptoms of psychotic symptoms in otherwise healthy individuals (Collizi et al. 2020).

Di Forti and colleagues showed that users who consume cannabis on a daily basis with an increased percentage of THC ≥10% are more than 5 times likely

to develop a psychotic disorder than those who do not use cannabis. Furthermore, they investigated how the high availability of highly potent cannabis species (THC ≥10%) affects the rates of psychotic disorders in 11 major European cities. They found that in Amsterdam, where cannabis types with an average THC of 29% are typically sold in cafes, up to 50% of new cases of developing psychotic disorder can be attributed to high-potency cannabis use. These data suggest that 50% of new cases of psychosis in Amsterdam could have been prevented if these individuals had not added the use of highly potent cannabis varieties to their group of risk factors for the development of psychosis. In the study, the three cities with the highest incidence rates of psychotic disorder - London, Amsterdam, and Paris - also had the highest rates of high-potency cannabis use in control samples representing their general population (Di Forti et al. 2019).

From the neurobiological aspect, it is a disorder of CB1 receptor signaling in the prefrontal cortex. Namely, CB1 receptors bind endogenous cannabinoids: anandamide (AEA) and 2-arachidonylglycerol (2-AG) and lead to CB1 receptor signaling, which inhibits the calcium currents necessary for the release of neurotransmitters at the presynaptic site (Lovinger 2008). CB1 receptor signaling induces inhibition of voltage-sensitive calcium channels and adenylate cyclase (Vogel et al. 1993), and activation of potassium channels and mitogen-activated protein kinase (Howlett et al. 2002). In this way, CB1 receptor signaling can modulate a wide range of neurotransmitters, including glutamate, GABA, dopamine, serotonin, and acetylcholine (Lovinger 2008) and has a homeostatic role in controlling over-excitation or inhibition (Marsicano et al. 2003, Katona et al. 2008). The effects of exogenous cannabinoids, such as Δ9-THC, depend on the levels of CB1 receptor occupancy with endogenous cannabinoids and the nature of endocannabinoid binding to the receptor. Δ9-THC "mimics" the action and effects of anandamide, which is a partial CB1 receptor agonist, as opposed to 2-AG, which is a full CB1 receptor agonist. In this regard, at synapses in which 2-AG is the major endocannabinoid, ago9-THC partial agonism may antagonize 2-AG activity. Thus, the psychoactive effects of Δ9-THC would not be fully antagonized by CB1 receptor antagonists (Heustis et al. 2001).

Disorders of CB1 receptor signaling in the prefrontal cortex are present in schizophrenia, and the use of THC markedly worsens symptoms (Caballero & Tseng 2012, D'Souza et al. 2005). The maturation of prefrontal cortex development is accompanied by a decrease in CB1 receptor function. Decreased CB1 receptor expression is associated with a functional decline in CB1 receptor signaling at excitatory synaptic transmission in the prefrontal cortex (Heng et al. 2011). Repeated exposure to THC leads to over-activation of the CB1 receptor which ultimately results in a decrease in cortical GABA-ergic function and an increase in the excitability of pyramidal neurons. The result is disinhibition and dysregulation, and disruption of the fine-tuning of the neural circuits of the prefrontal cortex (Mackie 2008).

Dr. Steven Laviolette presented research on the effects of THC on the brain of adolescents, doing a study on rodents. Adolescent exposure to THC has been found to cause changes in specific regions of the brain, namely in the prefrontal cortex and mesolimbic pathway, which are very similar to the abnormalities observed in schizophrenia (Conrod et al. 2019), which is in line with the above study.

The number of hospitalizations due to cannabis-induced psychotics is increasing worldwide. In Denmark, the incidence of cannabis-induced psychoses steadily increased from 2.8 / 100,000 in 2006 to 6.1 / 100,000 in 2016. There has also been a corresponding increase in the dual diagnosis of schizophrenia and cannabis use disorders. This increasing trend was not observed in other substances induced by psychosis. The increase in the incidence of cannabis-induced psychoses is accompanied by an increase in tetrahydrocannabinol levels in cannabis, as well as an increase in cannabis use (Hjorthøj et al. 2019).

Epidemiological data obtained from a retrospective study conducted in Portugal between 2000 and 2015 on the number of hospitalizations performed due to psychotic disorders associated with cannabis abuse or dependence show that the number of hospitalizations due to the development of the clinical picture of psychotic disorders and schizophrenia-associated with cannabis use increased 29.4 times during the study period, ie. from 20 to 588 hospitalizations per year. The number of dual diagnoses of psychotic disorder and schizophrenia-associated with cannabis use increased from 0.87% in 2000 to 10.60% in 2015. The obtained data on the increase in the number of hospitalizations could be related to the change in the pattern of cannabis consumption among the Portuguese population with an increasing frequency of moderate/large doses of cannabis consumption (Gonçalves-Pinho et al. 2019).

Nearly half of all clinically high-risk patients for psychotic development used cannabis, of which the prevalence of lifelong consumption was 48.7%, while the percentage of those currently using cannabis during the study was 25.8%, and 14.9% were have developed cannabis addiction (Farris et al. 2019), as evidenced by a systematic review article summarizing data from all studies on the subject published up to November 2018.

Cannabis use in early adulthood is prospectively associated with an increase in the number of prescribed psychotropic drugs, including antipsychotics, mood stabilizers, and antidepressants, according to data from a longitudinal Young study in Norway. The data were obtained from four waves of data collection between 1992 and 2006 and then merged with prescription information for psychotropic drugs from the Norwegian Prescription Database between 2007 and 2015 (Rognli et al. 2020).

Finally, in a recently published systematic review article that included 56 studies on the association between cannabis use and the development of psychosis published between 2009 and 2019, by van der Steur et al., is confirmed that frequent use of cannabis and consumption of highly potent varieties of cannabis increases the risk of developing psychosis. Furthermore, cannabis use reduces the age of onset of psychotic symptoms by 3 years and increases the risk of transition in individuals who are at a clinically high risk of developing a psychotic disorder. In conclusion, cannabis use is a risk factor for developing a psychotic disorder along with genetic predisposition and other environmental factors. These gene-environment interactions are complex and still unclear (van der Steur et al. 2020).

Cannabis use and depression

Longitudinal studies investigating the link between cannabis use and the development of depression have yielded mixed results. However, cannabis use, and especially heavy cannabis use, may be associated with an increased risk of developing depressive disorders (Lev-Ran et al. 2014).

Significantly focused is on the role of cannabis use in psychosis, less attention was paid to whether cannabis use was associated with an increased risk of common mental health disorders, such as depression and anxiety. Researchers from McGill University and Oxford University conducted a systematic review and meta-analysis of the best available evidence and analyzed 23,317 individuals (from 11 international studies) to determine whether cannabis use in young people was linked with depression, anxiety, and early adult suicide. A review of longitudinal and prospective studies on cannabis use among adolescents under 18 and the development of depression in young adulthood found that a high prevalence of cannabis-consuming adolescents in early adulthood is at risk for developing depression and suicidality attributable to cannabis use (Gobbi et al. 2019).

The prevalence of cannabis use in the United States increased from 2005 to 2017 among people with depression and without depression and was approximately twice as common among those suffering from depression (Pacek et al. 2019). The sample of the study consisted of 728,691 people over the age of 12, who had occasionally or daily consumed cannabis in the past month. People with depression experienced a faster decrease in risk perception, which may be related to a faster increase in any cannabis use in the past month in this group (Pacek et al. 2019).

Cannabis use and anxiety

Research on the link between cannabis use and the development of anxiety, especially in adolescents, has yielded mixed results, mainly due to different ways of measuring anxiety and diversity in good groups. According to the study conducted in 2019, 14.4-year-old adolescents who reported cannabis use within the past month had significantly more pronounced anxiety and emotional variability than adolescents who did not use cannabis (Rusby et al. 2018).

A review of available studies on the link of cannabis use and development of anxiety disorders found a positive association between anxiety and any cannabis use, occasional or daily, as well as between comorbid anxiety with depression and cannabis use (Kedzior & Laeber 2014).

A study conducted by researchers at Johns Hopkins Medicine shows that there is a difference in the way cannabis is consumed. In a small study involving subjects who occasionally used cannabis, the results showed that vapor use of cannabis increased the rate of short-term anxiety, paranoia, memory loss, and concentration compared with cannabis smoking when the doses were the same (Spindle et al. 2018).

On the other hand, there is a lot of interest in the possible anxiolytic effects of cannabis. The literature evaluating the efficacy of cannabis in the treatment of anxiety disorders is in its infancy. The data obtained through the questionnaires are mostly positive. Some animal studies support the anxiolytic effects of cannabis ingredients, yet other studies suggest the opposite results (Van Ameringen et al. 2019).

Cannabis use and cognition

Cannabis consumption is among a number of factors that may have interacted to influence brain development and mental function (Volkow et al. 2016). Cognitive changes have been linked to cannabis consumption, although their cause and longevity have been the subject of debate (Curran et al. 2016).

Empirical research conducted about the effects of acute and chronic cannabis use on cognitive functioning in the period from January 2004 to February 2015 was summarized in a 2016 review article. Cognitive impairment is present during acute cannabis intoxication, but also in non-intoxicated conditions during long-term use. Also, in acute and chronic cannabis use, verbal learning, memory, and attention are most consistently impaired, while psychomotor functions are impaired mainly in acute intoxication, however there is evidence of persistence of such impairments in chronic use and after discontinuation. Impairments of memory, attention, and some executive functions may be present even after prolonged abstinence, but the duration of damage or recovery of all cognitive domains remains insufficiently investigated. Early-onset cannabis consumption is often associated with poorer cognitive performance (Broyd et al. 2016).

What are the cognitive outcomes with long-term cannabis use in adults?

Despite advances in research, it remains unclear whether long-term cannabis use causes cognitive impairment after cessation of acute intoxication. The 2020

meta-analysis investigated the links between cognitive functioning and long-term (longer than 2 years), regular (more than 4 days per week), and recreational cannabis use in adults during the period of abstinence (more than 12 hours after consumption). Cannabis use is associated with a significant deficit of low amplitude in the area of executive functions, learning and memory, and global cognition, while there is a moderate deficit in decision making. Information processing, working memory, and attention were not significantly altered. The duration of cannabis use, years of onset, and prolonged abstinence (longer than 25 days) did not affect outcomes. The results of this study suggest that long-term and regular cannabis use are associated with small to moderate deficits in some cognitive domains (Lovell et al. 2020).

It is important to emphasize that cannabis use in patients with psychotic disorders is associated with poorer disease outcomes and psychosocial functioning, as confirmed by Seddon and colleagues in their cohort study of over a thousand patients during the first psychotic episode who used cannabis for one year. Those results of the study cannot be better explained by the age or sex of the patients, the duration of untreated psychoticism, the age of onset of psychotic development, ethnic characteristics, or the use of other psychoactive substances (Seddon et al. 2016).

Significantly, controlled cannabis use in patients with schizophrenia exacerbates positive psychotic symptoms but also increases cognitive deficit, suggesting a probable common underlying mechanism (D'Souza et al. 2005).

Cannabis use and insomnia

Research on the link between sleeping disturbances and cannabis use is in its infancy and has so far generally yielded mixed results (Babson et al. 2017). Previous studies suggest that the sedative effect of cannabis may improve sleep (Altman et al. 2019). So, Bachhuber et al. have investigated the effects of medical cannabis on sleep. Of the 1,000 respondents who reported the use of medical cannabis, in the period from April to October 2016 in the US state of Colorado, 74% of them stated that they take cannabis for the purpose of improving sleep. Among respondents who took cannabis for sleep, 84% found the use of medical cannabis very useful for regulating sleep, and most of those who took other over-the-counter (87%) or prescription sleep aids (83%) reported a reduction or discontinuation of these drugs (Bachhuber et al. 2019). Like alcohol, cannabis can improve subjective sleep complaints (Conroy & Arnedt 2014), especially if used over a short period of time (Angarita et al. 2016).

Up to 35% of adults in the United States suffer from sleep disorders, which are linked to a number of negative mental and physical health outcomes. The study, which included 311 individuals who also reported sleep-related problems and cannabis use, found that study participants expressed expectations that cannabis would reduce the incidence of sleep-related problems, including allowing them to sleep earlier, fall asleep faster and stay asleep longer. These results suggest that individuals believe that cannabis use can positively affect sleep quality (Altman et al. 2019).

However, tolerance is developed with chronic cannabis use to most of the effects observed at the beginning of cannabis consumption, including its sleep-inducing effects and slow strong improvement in sleep (Barratt et al. 1974), sleep efficiency does not improve (Pranikoff et al. 1973) or worsens (Karacan et al. 1976). Chronic cannabis use is associated with negative effects on sleep that are most pronounced during the contraction period (Angarita et al. 2016). Significantly, these effects are present during contraction even among individuals who have been exposed to low doses of cannabis (Haney et al. 1999), while they are common among regular cannabis users (Crowley et al. 1998). Sleep difficulties such as unusual dreams, insomnia, and poor sleep quality are present (Crowley et al. 1998). Symptoms of this type occur in 32% (Copersino et al. 2006) to 76% (Bolla et al. 2008) of persons during the contraction period.

Among the difficulty sleeping in chronic cannabis users is the presence of unusual dreams (Budney et al. 2003). Such dreams usually begin 1–3. days after cessation of cannabis use - when sleep quality is particularly poor (Budney et al. 2001, Budney et al. 2003, Vandrey et al. 2011), peak from 2–6 days, and the last 4–14 days (Budney et al. 2003) with coincide with other subjective sleep complaints. However, other large studies have revealed sleep difficulties that last for a long time, such as 43 days (Copersino et al. 2006), and especially strange dreams, which last as long as 45 days (Budney et al. 2003). There is a frequent return to the use of cannabis (or the use of alcohol or other sedatives) in order to improve sleep (Copersino et al. 2006). However, the positive effects of cannabis on sleep are reduced in chronic users compared to people who have just started using cannabis (Chait 1990), and on the other hand, the negative effects of cannabis on sleep are amplified with chronic use (Angarita et al. 2016). In this regard, chronic cannabis users are in situations where they need to increase cannabis use to achieve its subjective effects on improving sleep, while at the same time this increased use contributes to worsening overall sleep, which continues to lead to continued and increased cannabis use (Angarita et al. 2016).

Studies performed by using polysomnography during the cannabis withdrawal period have shown an increase in latency of the onset of sleep and wakefulness after the onset of sleep (Bolla et al. 2008, 2010). Total sleep time and sleep efficiency decrease (Adams & Barratt 1975, Bolla et al. 2008, 2010), while REM sleep increases (Feinberg et al. 1975). Changes in polysomnographic measurements can be recorded as early as the first night of abstinence (Feinberg et al. 1976), and are more pronounced in individuals who have frequently used

cannabis (more than 5 times per week in the last 3 months) (Bolla et al. 2008). During the first 2 weeks of abstinence, the changes progress (Bolla et al. 2010, Budney et al. 2003, Kouri & Pope 2000), and may last longer than 45 days during the abstinence period (Budney et al. 2003). Sleep disorders that occur during cannabis withdrawal may play a crucial role in treatment outcomes (Angarita et al. 2016), as relapse rates are higher when sleep problems and other withdrawal symptoms are present (Budney et al. 2004). Poor sleep quality during abstinence also contributes to relapse (Budney et al. 2003, 2008, Vandrey et al. 2011).

Sleep difficulties appear to be a predisposing factor for cannabis use, while initial sleep problems are a significant predictor of later use, doubling the risk of future cannabis use (Mednick et al. 2010).

ARE THERE NEUROBIOLOGICAL CONSEQUENCES OF CANNABIS USE IN ADOLESCENCE?

Adolescence is highly vulnerable for brain development and represents a critical period in which regulatory links are established between the cerebral cortex and deeper brain circuits, especially those related to emotion processing, which generally makes adolescents very vulnerable to psychoactive substance use disorders (Conrod et al. 2019).

The use of medical cannabis in Canada was legalized on July 30, 2001, while the Federal Law that came into force on October 17, 2018 and formally legalized the cultivation, possession, supply, and consumption of cannabis and its products and thus made Canada another state. in the world, after Uruguay, in which the use of cannabis is completely legalized (Sapra 2018). It is Canadian neuroscientists who are increasingly investigating the effects of cannabis on the adolescent's brain.

A study conducted in Montreal had a sample of 3,826 7th grade elementary school students during 2013 and 2014, who were tested for alcohol and cannabis use for 4 years each year, and their cognitive functions were assessed. The researchers found that substance use was associated with poor cognitive functioning, and cannabis use was associated with impaired working memory and inhibitory control, as well as impaired memory and perceptual judgment. Preliminary data suggest that cannabis use had a stronger effect on memory impairment in males, but that there was no gender difference when it came to inhibition control. Alcohol use has not been associated with impairment of these cognitive functions, suggesting that cannabis may have longer-term adverse effects than alcohol (Morin et al. 2019).

Laviolette et al., in their study of effects of THC on the brain of adolescents, suggest that THC exposure caused both affective and cognitive disorders, including deficits in social interactions, memory processing, and anxiety regulation (Laviollete et al. 2019).

Cannabis use in adolescence has been associated with reward and motivation-related behavioral changes. Paradoxically, this use has been proposed to increase motivation to use other drugs (the “gateway” hypothesis) and a potential “motivation syndrome” in which individuals are less willing to spend effort to get a reward. It is not known whether cannabis consumption in adolescents causes any of these responses or whether cannabis use is rather a symptom of an already existing condition that results in this behavior (Khokhar et al. 2019). The study was done on rats that were exposed to THC and their subsequent behavior was monitored. Differences in reward-related behavior have been reported, and changes have also been reported in the association between different brain regions, including those related to reward coding and motivation. These results suggest that adolescent cannabis exposure in rats may have produced long-term changes in the brain circuit that could contribute to behavioral changes observed after cannabis exposure (Khokhar et al. 2019).

“Noisy” brain

Prashad et al. measured dormant global cortical activity in cannabis users via EEG. They found that delta wave power was reduced and theta, beta, and gamma wave power was increased in cannabis users compared to the control group, suggesting enhanced dormant cortical activation and disinhibition of inhibitory functions that can disrupt cognitive processes. Increased cortical activity leads to a loss of neuronal refinement and efficiency, which may indicate the so-called. "Noisy" brain. These results suggest that there are differences in cortical activity and association between cannabis users and controls who do not use cannabis at rest, which may be associated with cognitive impairment (Prashad et al. 2018).

LEGAL STATUS OF CANNABIS

The issue of legalizing cannabis use varies from country to country, in terms of possession, distribution, and cultivation, as well as in terms of medical use of cannabis. These policies in most countries are regulated by the United Nations Single Convention on Narcotic Drugs, which was ratified in 1961, together with the 1971 Convention on Psychotropic Substances and the 1988 Convention on Illicit Traffic in Narcotic Drugs and Psychotropic Substances (Habibi & Hoffman 2018, Bewley-Taylor et al. 2016).

The recreational use of cannabis is banned in most countries. However, many have adopted a policy of decriminalization to make a simple possession a non-criminal offense. Others have much harsher penalties like some Asian and Middle Eastern countries where possession of even small amounts is punishable by imprisonment for several years (Powell 2018). Since 2012, eleven US states and Canada, and Uruguay have

passed a law that allows the production, processing, and use of cannabis for adults. Nine US states, Uruguay and Canada now allow legal retail sales of cannabis as well. In Washington DC and Vermont, it is legal for adults to grow cannabis for their personal use, but its sale remains illegal (Caulkins et al. 2015).

Medical cannabis is cannabis and cannabinoids that doctors prescribe to their patients (Murnion 2015). The U.S. National Institute on Drug Abuse defines medical cannabis as "the use of an entire plant of unprocessed marijuana or its essential extracts to treat symptoms of disease and other conditions." The cannabis plant has more than 400 different chemicals, of which about 70 are cannabinoids. Otherwise, typical approved drugs have only one or two chemicals (Anonymous 2016). The number of active chemicals in cannabis is one of the reasons why cannabis treatment is difficult to classify and study. However, the number of countries that have legalized the use of medical cannabis is on the rise. Some countries have more restrictive laws that allow the use of isolated cannabinoid drugs (Hall 2018). In Canada (Sapra 2018), Uruguay (Williams 2016), and the Netherlands (Williams 2016) cannabis can be purchased without a prescription. In Mexico, the THC content of medical cannabis is limited to one percent (Janikian 2017). The same limit applies in Switzerland, but no prescription is required for purchase (Depetris & Miller 2017). In the United States, the legality of medical cannabis varies from state to state, it is legal in 33 states, four (out of five) permanently inhabited American territories, and the District of Columbia (Anonymous 2018). An additional 14 states have more restrictive laws that allow the use of low THC products (Anonymous 2018).

Medical research on the use of cannabis as a treatment for various health conditions is becoming more and more frequent (Aklin & Bedard-Gilligan 2019), and the reasons for this trend include increasing support for cannabis use, the trend of legalization, and the perception of the medical use of cannabis.

WHAT EFFECTS CAN LEGALIZATION OF CANNABIS USE HAVE ON PUBLIC HEALTH?

Hall and Lynskey describe several events of public health significance that occurred in the United States after the legalization of cannabis use. Cannabis products are more potent, cheaper, and more accessible to adults. Adults are increasingly using cannabis, and daily cannabis use is on the rise. There are more and more examinations and hospitalizations of adults, but also adolescents and children related to cannabis use in the emergency departments. Short-term risks of cannabis legalization in the U.S. include (but are not limited to) memory impairment and psychomotor performance, and risky behaviors such as driving and working while intoxicated, which can result in car accidents and accidents at work. Long-term risks include adverse physical health outcomes (e.g., respiratory problems, testicular cancer, and abnormal fetal development), impaired cognitive performance and academic achievement, changes in brain integrity, mental disorders (e.g., development of psychosis, depression, anxiety disorders, and bipolar disorder), cannabis use disorders (development of addiction). Evidence is emerging that the use of highly potent varieties of cannabis, daily or near-daily use, and younger age at the onset of cannabis use exacerbate negative health outcomes in users (Hall & Lynskey 2020, Hasanović 2020).

What side effects can the legalization of cannabis increase?

Hall and Lynskey (2020) summarized the negative effects that can increase if harmful patterns of cannabis use increase as a result of legalization. The content is based on reviews of evidence on the harmful effects of cannabis on health (Babor et al. 2018, Hall et al. 2016, National Academies of Sciences Engineering and Medicine 2017) and analyzes of health outcomes to be monitored after legalization of cannabis (Fischer et al. 2019, Hall & Lynskey 2016, Windle et al. 2019).

Acute effects

Car accidents can increase if more cannabis users drive intoxicated or use more powerful cannabis products. More cannabis users can present themselves to emergency services with acute psychological disorders and psychotic symptoms if they use more powerful cannabis products such as extracts (Hall, Renström & Poznyak 2016). Side effects of cannabis on fetal development may increase if more women use cannabis during pregnancy, as appears in the United States (Volkow et al. 2019).

The relationship between cannabis use and the use of alcohol, tobacco and opioids will significantly affect the effects of cannabis legalization on public health (Choo & Emery 2017). The public health burden of these psychoactive substances could be reduced if cannabis became their substitute, while their effect could be enhanced if there was concomitant use of cannabis and these “drugs” (Windle et al. 2019).

Chronic effects

More frequent cannabis use with a higher concentration of THC can increase the prevalence of cannabis addiction, i.e. more cannabis users will lose control over recreative cannabis use despite the fact that increased cannabis use causes them significant harm.

Cannabis users, who use it daily, have impaired cognitive performance that decreases with abstinence. Adolescents and young people who are regularly intoxicated with marijuana during schooling have poorer educational outcomes. Cognitive impairment associated with cannabis can also occur in older adults who regularly use cannabis for recreational purposes (Aurer et al. 2016).

Daily cannabis use has been associated with an increased risk of psychotic symptoms or a diagnosis of schizophrenic psychosis in prospective epidemiological studies (Marconi et al. 2016). The risks of psychotic symptoms are higher in those who start using cannabis in adolescence, in those who use it more often and for longer, and those who use strains with a high concentration of THC and/or a low concentration of cannabidiol (Di Forti et al. 2015). Psychotic symptoms occur on average two years earlier in regular cannabis users, and people with psychosis who continue to use cannabis have more frequent episodes and longer periods of hospitalization due to their illnesses. In larger European cities, an association between the average potency of cannabis and the incidence of psychosis has been reported (Large et al. 2011, Schoeler et al. 2016, Di Forti et al. 2019).

Cannabis users who take it longer and in larger amounts may develop hyperemesis syndrome, with severe abdominal pain and cyclic vomiting (Allen et al. 2004). This syndrome is more common in everyday cannabis users in the absence of any other medical reason. The discomfort disappears after bathing in hot water, or when users refrain from using cannabis but can recur if they start consuming cannabis again. The number of deaths attributed to complications of this syndrome is small (Khattar & Routsolias 2018, Nourbakhsh et al. 2019).

Research suggests that smoking cannabis with a high concentration of THC may increase the risk of cardiovascular disease in young "heavy" cannabis smokers. Middle-aged men who have had a myocardial infarction may have angina if they smoke cannabis and with an increased risk of relapse if they continue to use cannabis (Mittleman et al. 2001, Mukamal et al. 2008).

Smokers who smoke only cannabis report more coughs, sputum, and bronchial wheezing than people who do not smoke cannabis, and these symptoms are reduced if they stop smoking cannabis. However, cannabis smokers do not appear to have a higher risk of chronic obstructive pulmonary disease than non-smokers (Moore et al. 2005, Hancox et al. 2015).

Systemic tests have not found an association between cannabis use and head and / or neck or lung cancer (Zhang et al. 2015). In contrast, a meta-analysis of three studies revealed a small increase in testicular cancer risk in high-frequency cannabis users and in those who had used cannabis for ten years or more (Gurney et al. 2015).

KEY ARGUMENTS FOR LOBBYING CANNABIS LEGALIZATION

Hall and Lynskey (2020) point out that there are two key arguments for lobbying for legalization: a) reduced access to adolescents and b) the safety of available cannabis which is less potent due to its state-controlled active ingredient, tetrahydrocannabinol. But what do the available epidemiological data indicate? In December 2019, the US Agency for Substance Abuse and Mental Health (SAMHSA) published data from their national survey on drug use and health for 2017-2018 year on the increase in the number of young people who use cannabis in countries where recreational cannabis use is legalized compared to countries where the use is illegal. The number of young people using cannabis is 30% higher than last year, last month's use increased by 40%, while the number of young people using cannabis for the first time is also increasing by 30% (US Substance Abuse and Mental Health Services Administration 2019). Canada, Uruguay, and the United States have legalized the use of cannabis for adults, while its use has remained illegal for adolescents, who continue to buy it from criminal gangs and risk prosecution for their use. Furthermore, highly potent edible types of cannabis are often available, to which the price has also dropped. For example, in Washington, where cannabis use among adolescents is increasing daily, the use of more potent varieties of cannabis is also growing, in which the THC content reaches a THC content of 70% or more (Smart et al. 2017).

And in the end, none of the countries that have legalized recreational cannabis use, nor those that intend to follow it, have invested enough resources in educational campaigns to educate the general public, especially young people, about the effects of cannabis on brain development, academic achievements and the risk addiction developing. Therefore, the freedom that comes from a legal approach to cannabis could only be an illusion if it is not accompanied by knowledge of its harmful effects (Di Forti 2020).

CONCLUSION

In this paper, we examined the effects of cannabis use on psychiatric disorders. A review of the legal status of cannabis use in the world was also made. The possible consequences of cannabis legalization on the public health system were also considered, based on experiences from countries where legalization has already been done. The evidence cited in this article suggests that strong claims about the need to legalize cannabis are still questionable, and may, even in the long run, remain mixed, inconclusive, or even contradictory. Political interference in this issue can trigger a wide range of unintended but profound and lasting consequences for the health system and the health of the individual. Future research will need to optimize pharmacological manipulation by signaling the endocannabinoid system, before any medical product associated with cannabis to treat psychosis and cognitive impairment actually comes to market. We recommend further research on this topic and data collection with an emphasis on the effects and consequences of cannabis use on mental health, and in particular the benefits and harmful effects of medical cannabis use

Acknowledgements: *None.*

Conflict of interest: *None to declare.*

Contribution of individual authors:

Nera Žigić: conception and design of the manuscript, collecting data and literature searches, analyses and interpretation of literature, manuscript preparation and writing the paper; and gave final approval of the version to be submitted.

Mevludin Hasanović: made substantial contributions to conception and design, literature searches, participated in revising the manuscript and gave final approval of the version to be submitted.

Izet Pajević: made substantial contributions to conception and design, and interpretation of data, participated in revising the manuscript and gave final approval of the version to be submitted.

Miro Jakovljević: made substantial contributions to conception and design, and interpretation of data, participated in revising the manuscript and gave final approval of the version to be submitted.

References

1. *Adams BI & Martin RB: Cannabis: pharmacology and toxicology in animals and humans. Addiction 1996; 91:1585-614*
2. *Adams PM & Barratt ES: Effect of chronic marijuana administration of stages of primate sleep–wakefulness. Biol Psychiatry 1975; 10:315–22*
3. *Aklin WM & Bedard-Gilligan M: Non-pharmacological Treatments for Cannabis Use Disorders. Cannabis Use Disorders 2019; 229-236*
4. *Allen JH, de Moore GM, Heddle R & Twartz JC: Cannabinoid hyperemesis: cyclical hyperemesis in association with chronic cannabis abuse. Gut 2004; 53:1566-70. doi: 10.1136/gut.2003.036350. PMID: 15479672; PMCID: PMC1774264*
5. *Altman BR, Mian M, Slavin MN & Earleywine M: Cannabis Expectancies for Sleep. Cannabis Expectancies for Sleep. Journal of psychoactive drugs 2019; 51:1-8*
6. *Angarita GA, Emadi N, Hodges S & Morgan PT: Sleep abnormalities associated with alcohol, cannabis, cocaine, and opiate use: a comprehensive review. Addiction science & clinical practice 2016; 11*
7. *Anonymous: "Up in Smoke: Does Medical Marijuana Work?" Consumer reports 2016. https://www.consumerreports.org/medical-marijuana/does-medical-marijuana-work/ Approached 02.08.2021*
8. *Anonymous: "State Medical Marijuana Laws". National Conference of State Legislatures 2018. https://www.ncsl.org/research/health/state-medical-marijuana-laws.aspx Approached 02.08.2021*
9. *Appendino G, Gibbons S, Giana A, Pagani A, Grassi G, Stavri M et al.: Antibacterial Cannabinoids from Cannabis sativa: A Structure-Activity Study. J Nat Prod 2008; 71:1427-30*
10. *Arseneault L, Cannon M, Poulton R, Murray R, Caspi A & Moffitt TE: Cannabis use in adolescence and risk for adult psychosis: longitudinal prospective study. BMJ 2002; 325:1212*
11. *Arseneault L, Cannon M, Witton J & Murray R: Causal association between cannabis and psychosis: examination of the evidence. The British Journal of Pschiatry 2004*
12. *Auer R, Vittinghoff E, Yaffe K, Künzi A, Kertesz SG, Levine DA, Albanese E, Whitmer RA, Jacobs DR Jr, Sidney S, Glymour MM & Pletcher MJ: Association Between Lifetime Marijuana Use and Cognitive Function in Middle Age: The Coronary Artery Risk Development in Young Adults (CARDIA) Study. JAMA Intern Med 2016; 176:352-61. doi: 10.1001/jamainternmed.2015.7841. PMID: 26831916, PMCID: PMC5109019*
13. *Babor T, Caulkins JP, Fischer B et al.: Drug policy and the public good, 2nd ed. New York: Oxford University Press, 2018*
14. *Babson KA, Sottile J & Morabito D: Cannabis, Cannabinoids, and Sleep: a Review of the Literature. Curr Psychiatry Rep 2017; 19:23*
15. *Bachhubert M, Arnsten JH & Wurm G: Use of Cannabis to Relieve Pain and Promote Sleep by Customers at an Adult Use Dispensary. Journal of psychoactive drugs 2019; 51*
16. *Barrat E S, Beaver W & White R: The effects of marijuana on human sleep patterns. Biol Psychiatry 1974; 8: 47-54*
17. *Ben Amar M & Potvin S: Cannabis and Psychosis: What is the Link? Journal of psychoactive drugs 2007; 39:131-42*
18. *Bewley-Taylor D, Jelsma M, Rolles S et al.: "Cannabis regulation and the UN drug treaties" 2016*
19. *Bolla K, Lesage S, Gamaldo C, Neubauer D, Funderbuck F, Lud Cadet J et al.: Sleep disturbance in heavy marijuana users. Sleep 2008; 31: 901–908*
20. *Bolla KI, Lesage SR, Gamaldo CE, Neubauer DN, Wang NY, Funderburk FR et al.: Polysomnogram changes in marijuana users who report sleep disturbances during prior abstinence. Sleep Med 2010; 11:882–9*
21. *Bolla K, Lesage S, Gamaldo C, Neubauer D, Funderbuck F, Lud Cadet J et al.: Sleep disturbance in heavy marijuana users. Sleep 2008; 31: 901–908*
22. *Broyd SJ, van Hell HH, Beale C, Yücel M & Solowij N: Acute and Chronic Effects of Cannabinoids on Human Cognition-A Systematic Review. Biol Psychiatry 2016; 79:557-67*
23. *Budney AJ, Hughes JR, Moore BA & Novy PL: Marijuana abstinence effects in marijuana smokers maintained in their home environment. Arch Gen Psychiatry 2001; 58:917–924*
24. *Budney AJ, Moore BA, Vandrey RG & Hughes JR: The time course and significance of cannabis withdrawal. J Abnorm Psychol 2003; 112:393–402*
25. *Budney AJ, Hughes JR, Moore BA & Vandrey R: Review of the validity and significance of cannabis withdrawal syndrome. Am J Psychiatry 2004; 161:1967–77*
26. *Caballero A & Tseng KY: Association of cannabis use during adolescence, prefrontal CB1 receptor signaling and schizophrenia. Frontiers in Pharmacology 2012*
27. *Caspi A, Moffitt TE, Cannon M, McClay J, Murray R, Harrington H et al.: 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. Biol. Psychiatry 2005, 57*
28. *Chait LD: Subjective and bihevioral effects of marijuana the morning after smoking. Psychopharmacology 1990; 100: 328-33*
29. *Choo EK & Emery SL: Clearing the haze: the complexities and challenges of research on state marijuana laws. Ann NY Acad Sci 2017; 1394:55-73*

30. Colizzi M, Ruggeri M & Bhattacharyya S: Unraveling the Intoxicating and Therapeutic Effects of Cannabis Ingredients on Psychosis and Cognition. Front Psychol 2020; 11: 833
31. Conrod P, Laviolette S & Balodis I: Cannabis affects male teenagers' memory more than females'.The Canadian Association for Neuroscience 2019
32. Conroy DA & Arnedt JT: Sleep and Substance Use Disorders: An Update. Current Psychiatry Reports 2014: 16
33. Copersino ML, Boyd SJ, Tashkin DP, Huestis MA, Heishman SJ, Dermand JC et al.: Cannabis withdrawal among non-treatment- seeking adult cannabis users. Am J Addict 2006; 15:8–14
34. Crowley TJ, Macdonald MJ, Whitmore EA & Mikulich SK: Cannabis dependence, withdrawal, and reinforcing effects among adolescents with conduct symptoms and substance use disorders. Drug Alcohol Depend 1998; 50:27–37
35. Curran HV, Freeman TP, Mokrysz C, Lewis DA, Morgan CJ & Parsons LH: Keep off the grass? Cannabis, cognition and addiction. Nat Rev Neurosci 2016; 17:293–306
36. Depetris M & Miller J: "Swiss cannabis entrepreneurs develop craving for low-potency pot". Reuters 2017
37. Di Forti M, Marconi A, Carra E, Fraietta S, Trotta A, Bonomo M, Bianconi F, Gardner-Sood P, O'Connor J, Russo M, Stilo SA, Marques TR, Mondelli V, Dazzan P, Pariante C, David AS, Gaughran F, Atakan Z, Iyegbe C, Powell J, Morgan C, Lynskey M & Murray RM: Proportion of patients in south London with first-episode psychosis attributable to use of high potency cannabis: a case-control study. Lancet Psychiatry 2015; 2:233-8. doi:10.1016/S2215-0366(14)00117-5. Epub 2015 Feb 25. PMID: 26359901
38. Di Forti M, Quattrone D, Freeman TP, Tripoli G, Gayer-Anderson C, Quigley H, Rodriguez V, Jongsma HE, Ferraro L, La Cascia C, La Barbera D, Tarricone I, Berardi D, Szöke A, Arango C, Tortelli A, Velthorst E, Bernardo M, Del-Ben CM, Menezes PR, Selten JP, Jones PB, Kirkbride JB, Rutten BP, de Haan L, Sham PC, van Os J, Lewis CM, Lynskey M, Morgan C, Murray RM & EU-GEI WP2 Group: The contribution of cannabis use to variation in the incidence of psychotic disorder across Europe (EU-GEI): a multicentre case-control study. Lancet Psychiatry 2019; 6:427-436. doi: 10.1016/S2215-0366(19)30048-3. Epub 2019 Mar 19. PMID: 30902669
39. D'Souza DC, Perry E, MacDougall L, Ammerman Y, Cooper T, Wu Y-T et al.: The psychotomimetic effects of intravenous delta-9-tetrahydrocannabinol in healthy individuals: implications for psychosis. Neuropsychopharmacology 2004; 29:1558-72
40. D'Souza DC, Abi-Saab WM, Madonick S, Forselius-Bielen K, Doersch A, Braley G et al.: Delta-9-tetrahydrocannabinol effects in schizophrenia: implications for cognition, psychosis, and addiction. Biol. Psychiatry 2005; 57:594–608
41. Elsaid S, Kloiber S & Le Foll B: Effects of cannabidiol (CBD) in neuropsychiatric disorders: A review of preclinical and clinical findings. Prog Mol Biol Transl Sci 2019; 167:25-75
42. Farris MS, Shakeel MK & Addington J: Cannabis use in individuals at clinical high-risk for psychosis: a comprehensive review. Soc Psychiatry Psychiatr Epidemiol 2019
43. Feinberg I, Jones R, Walker JM, Caveness C & Floyd T: Effects of marijuana extract and tetrahydrocannabinol on electroencephalographic sleep patterns. Clin Pharmacol Ther 1976; 19:782-94
44. Feinberg I, Jones R, Walker JM, Caveness C & March J: Effects of high dosage delta-9-tetrahydrocannabinol on sleep patterns in man. Clin Pharmacol Ther 1975; 17:458-66
45. Fischer B, Russell C, Rehm J et al.: Assessing the public health impact of cannabis legalization in Canada: core outcome indicators towards an 'index' for monitoring and evaluation. J Public Health 2019; 41:412-21
46. Ford TC, Hayley AC, Downey LA & Parrott AC: Cannabis: An Overview of its Adverse Acute and Chronic Effects and its Implications. Curr Drug Abuse Rev 2017; 10:6-18
47. Gardner E & Lowinson JH: Marijuana's interaction with brain reward systems: update 1991. Pharmacol Biochem Behav 1991; 40:571–580
48. Gobbi G, Atkin T, Zytynski T et al.: Association of Cannabis Use in Adolescence and Risk of Depression, Anxiety, and Suicidality in Young Adulthood.A Systematic Review and Meta-analysis. JAMA Psychiatry 2019; 76:426-434
49. Gonçalves-Pinho M, Bragança M & Freitas A: Psychotic disorders hospitalizations associated with cannabis abuse or dependence: A nationwide big data analysis. Int J Methods Psychiatr Res 2020; 29:e1813. doi: 10.1002/mpr.1813. Epub 2019 Dec 5. PMID: 31808250; PMCID: PMC7051837
50. Gurney J, Shaw C, Stanley J, Signal V & Sarfati D: Cannabis exposure and risk of testicular cancer: a systematic review and meta-analysis. BMC Cancer 2015; 15:897. doi:10.1186/s12885-015-1905-6. PMID: 26560314; PMCID: PMC4642772
51. Habibi R & Hoffman S: Legalizing Cannabis Violates the UN Drug Control Treaties, But Progressive Countries Like Canada Have Options. Ottawa Law Review, Forthcoming, 2018
52. Haney M, Ward AS, Comer SD, Foltin RW & Fischman MW: Abstinence symptoms following smoked marijuana in humans. Psychopharmacology 1999; 141:395–404
53. Hall W: "Medical use of cannabis and cannabinoids" - Questions and answers for policymaking. European Monitoring Centre for Drugs and Drug Addiction. Luxembourg: Publications Office of the European Union, 2018
54. Hall WD, Renström M & Poznyak V: The health and social effects of nonmedical cannabis use. Geneva: World Health Organization, 2016
55. Hall WD & Lynskey M: Evaluating the public health impacts of legalizing recreational cannabis use in the United States. Addiction 2016; 111:1764-73
56. Hall W & Lynskey M: Assessing the public health impacts of legalizing recreational cannabis use: the US experience. World Psychiatry 2020; 19:179-186. doi:10.1002/wps.20735. PMID:32394566, PMCID: PMC7215066
57. Hancox RJ, Shin HH, Gray AR, Poulton R & Sears MR: Effects of quitting cannabis on respiratory symptoms. Eur Respir J 2015; 46:80-7. doi:10.1183/09031936.00228914. Epub 2015 Apr 2. PMID: 25837035, PMCID: PMC4780250
58. Hasanović M: Prof. dr. Mevludin Hasanović za "Avaz": Političari postali žrtva lobija. Razgovarala Almasa Hadžić 09.02.2020. https://avaz.ba/vijesti/intervju/547699/prof-dr-mevludin-hasanovic-za-avaz-politicari-postali-zrtva-lobija
59. Heng L, Beverley JA, Steiner H & Tseng KY: Differential developmental trajectories for CB1 cannabinoid receptor expression in limbic/associative and sensorimotor cortical areas. Synapse 2011; 65:278–286

60. Herkenham M, Lynn AB, Little MD, Johnson MR, Melvin LS et al.: Cannabinoid receptor localization in brain. Proc Natl Acad Sci U S A 1990; 87:1932–6
61. Hjorthøj C, Larsen MO, Kejser Starzer MS & Nordentoft S: Annual incidence of cannabis-induced psychosis, other substance-induced psychoses and dually diagnosed schizophrenia and cannabis use disorder in Denmark from 1994 to 2016. Psychological Medicine 2019, 1-6
62. Howlett AC, Barth F, Bonner TI, Cabral G, Casellas P, Devane WA et al.: International union of pharmacology. XXVII. Classification of cannabinoid receptors. Pharmacol Rev 2002; 54:161–202
63. Huestis MA, Gorelick DA, Heishman SJ, Preston KL, Nelson RA, Moolchan ET et al.: Blockade of effects of smoked marijuana by the CB1-selective cannabinoid receptor antagonist SR141716. Arch Gen Psychiatry 2001; 58:322-8
64. Janikian M: "Legal Pot In Mexico: Everything You Need to Know". Rolling Stone 2017
65. Johnston LD, O'Malley PM, Bachman JG & Schulenberg JE: Monitoring the future national survey results on drug use, 1975–2012: Volume I, Secondary school students. Ann Arbor: Institute for Social Research, The University of Michigan, 2013
66. Katona I & Freund TF: Endocannabinoid signaling as a synaptic circuit breaker in neurological disease. Nat. Med 2008; 14:923–930
67. Karacan I, Fernandez-Salas A, Coggins WJ, Carter WE, Williams RL, Thornby JI et al.: Sleep electroencephalographic- electrooculographic characteristics of chronic marijuana users: part I. Ann N Y Acad Sci 1976; 282:348–74
68. Kedzior KK &Laeber LT: A positive association between anxiety disorders and cannabis use or cannabis use disorders in the general population- a meta-analysis of 31 studies. BMC Pschiatry 2014; 136
69. Khattar N & Routsolias JC: Emergency department treatment of cannabinoid hyperemesissyndrome: a review. Am J Ther 2018; 25:e357-61
70. Large M, Sharma S, Compton MT, Slade T & Nielssen O: Cannabis use and earlier onset of psychosis: a systematic meta-analysis. Arch Gen Psychiatry 2011; 68:555-61. doi: 10.1001/archgenpsychiatry.2011.5. Epub 2011 Feb 7. PMID: 21300939
71. Lev-Ran S, Roerecke M, LeFoll B, George TP, McKenzie K & Rehm J: The association between cannabis use and depression: a systematic review and meta-analysis of longitudinal studies. Psych Med 2014; 44:797-810
72. Lovell ME, Akhurst J, Padgett C, Garry MI & Matthews A: Cognitive outcomes associated with long-term, regular, recreational cannabis use in adults: A meta-analysis. Exp Clin Psychopharmacol 2020; 28:471-494
73. Lovinger DM: Presynaptic modulation by endocannabinoids. Handb. Exp. Pharmacol 2008; 435–477
74. Kouri EM & Pope HG Jr: Abstinence symptoms during withdrawal from chronic marijuana use. Exp Clin Psychopharmacol 2000; 8:483–92
75. Marsicano G, Goodenough S, Monory K, Hermann H, Eder M, Cannich A et al.: CB1 cannabinoid receptors and on-demand defense against excitotoxicity. Science 2003; 302:84–88
76. Mackie K: Cannabinoid Receptors: Where They are and What They do. Journal of Neuroendocrinology 2008; 20(Suppl 1):10-4. doi: 10.1111/j.1365-2826.2008.01671.x. PMID: 18426493
77. Marconi A, Di Forti M, Lewis CM, Murray RM & Vassos E: Meta-analysis of the Association Between the Level of Cannabis Use and Risk of Psychosis. Schizophr Bull 2016; 42:1262-9. doi: 10.1093/schbul/sbw003. Epub 2016 Feb 15. PMID: 26884547, PMCID: PMC4988731
78. Mednick SC, Christakis NA & Fowler JH: The spread of sleep loss influences drug use in adolescent social networks. PLoS One 2010; 5: e9775
79. Mehmedic Z, Chandra S, Slade D et al.: Potency trends of Δ9-THC and other cannabinoids in confiscated cannabis preparations from 1993 to 2008. J Forensic Sci 2010; 55:1209-1217
80. Mittleman MA, Lewis RA, Maclure M, Sherwood JB & Muller JE: Triggering myocardial infarction by marijuana. Circulation 2001; 103:2805-9. doi:10.1161/01.cir.103.23.2805. PMID: 11401936
81. Moore BA, Augustson EM, Moser RP & Budney AJ: Respiratory effects of marijuana and tobacco use in a U.S. sample. J Gen Intern Med 2005; 20:33-7. doi:10.1111/j.1525-1497.2004.40081.x. PMID: 15693925, PMCID: PMC1490047
82. Moore TH, Zammit S, Lingford-Hughes A, Barnes TR, Jones PB, Burke M et al.: Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review. Lancet 2007; 370:319–328
83. Morin J-FG, Afzali MH, Bourque J, Stewart SH, Séguin JR, O'Leary-Barrett M et al.: A Population-Based Analysis of the Relationship Between Substance Use and Adolescent Cognitive Development. Am J Psychiatry 2019; 176:98-106
84. Mukamal KJ, Maclure M, Muller JE & Mittleman MA: An exploratory prospective study of marijuana use and mortality following acute myocardial infarction. Am Heart J 2008; 155:465-70. doi: 10.1016/j.ahj.2007.10.049. PMID: 18294478, PMCID: PMC2276621
85. Munro S, Thomas KL & Abu-Shaar M: Molecular characterization of a peripheral receptor for cannabinoids. Nature 1993; 365:61–65
86. Murnion B: Medicinal cannabis. Australian Prescriber 2015; 38:212-5
87. National Academies of Sciences Engineering and Medicine: The health effects of cannabis and cannabinoids: the current state of evidence and recommendations for research. Washington: National Academies Press for the National Academies of Sciences Engineering and Medicine, 2017
88. Nelong TF, Jenkins B, Perreault ML & Khokhar JY: Extended Attenuation of Corticostriatal Power and Coherence after Acute Exposure to Vapourized Δ9-Tetrahydrocannabinol in Rats. The Canadian Journal of Addiction 2019; 10: 60-66
89. Nicholson AN, Turner C, Stone BM & Robson PJ: Effect of D-9-Tetrahydrocannabinol and Cannabidiol on Nocturnal Sleep and Early-Morning Behavior in Young Adults. Journal of Clinical Psychopharmacology 2004; 24:305-313
90. Nourbakhsh M, Miller A, Gofton J, Jones G & Adeagbo B: Cannabinoid Hyperemesis Syndrome: Reports of Fatal Cases. J Forensic Sci 2019; 64:270-274. doi: 10.1111/1556-4029.13819. Epub 2018 May 16. PMID: 29768651
91. Oldani L & Grancini B: Cannabis-Induced Psychosis. Clinical Cases in Psychiatry:Integrating Translational Neuroscience Aporoaches. Cham: Springer 2018; 115-135
92. Pacek LR, Weinberger AH, Jiaqi Z & Goodwin RD: Rapid increase in the prevalence of cannabis use among people with depression in the United States, 2005–17: the role of differentially changing risk perceptions. Addiction 2019

93. Pajević I, Hasanović M, Žigić N, Pajević A & Avdić L: Do Cannabis and Cannabinoids have a psychopharmacotherapeutic effect? Psychiatr Danub 2021; 33(Suppl. 4): S1196-1203
94. Parsons LH & Hurd YH: Endocannabinoid signaling in reward and addiction. Nature Reviews Neuroscience 2015; 16:579-594
95. Paul SE, Hatoum AS, Fine JD, Johnson EC, Hansen I, Karcher NR, Moreau AL, Bondy E, Qu Y, Carter EB, Rogers CE, Agrawal A, Barch DM & Bogdan R: Associations Between Prenatal Cannabis Exposure and Childhood Outcomes: Results From the ABCD Study. JAMA Psychiatry 2020; 23. doi:10.1001/jamapsychiatry.2020.2902. Epub ahead of print. PMID: 32965490
96. Sadock BJ, Sadock A & Sadock VA: Kaplan & Sadock' Pocket Handbook of Clinical Psychiatry. Sixth Edition. Philadelphia: Wolters Kluwer, 2019
97. Powell B: "The 7 Countries with the Strictest Weed Laws". High Times 2018
98. Pranikoff K, Karacan I, Larson EA, Williams RL, Thornby JI, Hursch CJ: Effects of marijuana smoking on the sleep EEG. Preliminary studies JFMA 1973; 60:28–31
99. Prashad S, Dedrick E & Filbey F: Cannabis users exhibit increased cortical activation during resting state compared to non-users. NeuroImage 2018; 179:176-86
100. Rognli EB, Bramness JG & von Soest T: Cannabis use in early adulthood is prospectively associated with prescriptions of antipsychotics, mood stabilizers, and antidepressants. Acta Psychiatr Scand 2020; 141:149-156
101. Rusby JC, Westling E, Crowley R & Light JM: Legalization of recreational marijuana and community sales policy in Oregon: Impact on adolescent willingness and intent to use, parent use, and adolescent use. Psychol Addict Behav 2018; 32:84-92
102. Sapra B: "Canada becomes second nation in the world to legalize marijuana". CNN 2018
103. Schoeler T, Monk A, Sami MB, Klamerus E, Foglia E, Brown R, Camuri G, Altamura AC, Murray R & Bhattacharyya S: Continued versus discontinued cannabis use in patients with psychosis: a systematic review and meta-analysis. Lancet Psychiatry 2016; 3:215-25. doi: 10.1016/S2215-0366(15)00363-6. Epub 2016 Jan 15. PMID: 26777297
104. Seddon JL, Birchwood M, Copello A, Everard L, Jones PB, Fowler D et al.: Cannabis Use Is Associated With Increased Psychotic Symptoms and Poorer Psychosocial Functioning in First-Episode Psychosis: A Report From the UK National EDEN Study. Schizophr Bull 2016, 42:619-25
105. Sewell AR, Poling J & Sofuoglu M: The Effect of Cannabis Compared with Alcohol on Driving. The American Journal of Addiction 2010
106. Sideli L, Quigley H, la cascia C & Murray R: Cannabis Use and the Risk of Psychosis and Affective Disorders. Journal of Dual Diagnosis 2019; 16:1-21
107. Spindle TR, Cone EJ, Schlienz NS, Mitchell JM et al.: Acute Effects of Smoked and Vaporized Cannabis in Healthy Adults Who Infrequently Use Cannabis. JAMA Network Open 2018; 1
108. Seedon JL, Birchwood M, Copello A, Everard L, Jones PB, Fowler D et al.: Cannabis Use Is Associated With Increased Psychotic Symptoms and Poorer Psychosocial Functioning in First-Episode Psychosis: A Report From the UK National EDEN Study. Schizophr Bull 2016; 42:619-25
109. Szkudlarek HJ, Desai SJ, Renard J, Pereira B, Norris C, Jobson CEL et al.: Δ-9-Tetrahydrocannabinol and Cannabidiol produce dissociable effects on prefrontal cortical executive function and regulation of affective behaviors. Neuropsychopharmacology 2019; 44:817–825
110. van der Steur SJ, Batalla A & Bossong MG: Factors Moderating the Association between Cannabis Use and Psychosis Risk: A Systematic Review. Brain Sci 2020; 10:97
111. Vandrey R, Smith MT, McCann UD, Budney AJ & Curran EM: Sleep disturbance and the effects of extended release zolpidem during cannabis withdrawal. Drug Alcohol Depend 2011; 117:38–44
112. Williams S: "10 Countries (Aside From the U.S.) Where Some Form of Medical Marijuana Is Legal". The Motley Fool 2017
113. Windle SB, Wade K, Filion KB, Kimmelman J, Thombs BD, Eisenberg MJ. Potential harms from legalization of recreational cannabis use in Canada. Can J Public Health 2019; 110:222-226. doi: 10.17269/s41997-018-00173-1. Epub 2019 Feb 13. PMID: 30759307; PMCID: PMC6964625
114. Vogel Z, Barg J, Levy R, Saya D, Heldman E & Mechoulam R: Anandamide, a brain endogenous compound, interacts specifically with cannabinoid receptors and inhibits adenylate cyclase. J. Neurochem 1993; 61:352–355
115. Volkow ND, Han B, Compton WM et al.: Self-reported medical and nonmedical cannabis use among pregnant women in the United States. JAMA 2019; 322:167-9
116. Volkow ND, Swanson JM, Evins AE, DeLisi LE, Meier MH, Gonzales R et al.: Effects of Cannabis Use on Human Behavior, Including Cognition, Motivation, and Psychosis: A Review. JAMA Psychiaty 2016; 73:292-7
117. Zammit S, Allebeck P, Andreasson S, Lundberg I & Lewis G: Self-reported cannabis use as a risk factor for schizophrenia in Swedish conscripts of 1969: historical cohort study. BMJ 2002; 325:1199. doi:10.1136/bmj.325.7374.1199. PMID:12446534; PMCID: PMC135490
118. Zhang LR, Morgenstern H, Greenland S, Chang SC, Lazarus P, Teare MD, Woll PJ, Orlow I & Cox B: Cannabis and Respiratory Disease Research Group of New Zealand, Brhane Y, Liu G & Hung RJ: Cannabis smoking and lung cancer risk: Pooled analysis in the International Lung Cancer Consortium. Int J Cancer 2015; 136:894-903. doi: 10.1002/ijc.29036. Epub 2014 Jun 30. PMID: 24947688; PMCID: PMC4262725

Correspondence:
Nera Žigić, MD
Department of Psychiatry, University Clinical Center Tuzla
Ul. Rate Dugonjića bb, 75 000 Tuzla, Bosnia and Herzegovina
E-mail: near.hodzic@hotmail.com