DO CANNABIS AND CANNABINOIDS HAVE A PSYCHOPHARMACOTHERAPEUTIC EFFECT?

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SUMMARY

Backgrounds: *Written historical evidence reveals that Cannabis sativa has been used medically, recreationally and spiritually for more than five centuries in many cultures. It is considered the most-used plant-based psychoactive substance with millions of different usages across the world. To review what the studies, conducted over the past two decades, indicate about effects of the cannabis on physical and mental health as well as the impact on social functioning.*

Methods: *We selected literature review using PubMed resources, to summarize the findings of the existing publications on cannabis and cannabinoids and their possible psychopharmacological therapeutic effects only.*

Results: *Research supports cannabis' clear acute effect on neurocognition, while non-acute effects for prolonged use of marijuana are unclear and still insufficiently explored. Due to cannabidiol's (CBD) safety and tolerability, the absence of psychoactive or cognitive effects, the existence of clinical trials with positive results and its broad pharmacological spectrum, CBD is a cannabinoid whose initial results will likely lead to implementation into clinical practice. The fact that the results of previous studies establish the claim of CBD as an antipsychotic and anxiolytic, makes the above developments even more likely. However, long-term, double-blind, placebo studies with samples of patients with different psychotic and anxiety disorders are still necessary. Likewise, due to CBD's biphasic effects, determining an adequate therapeutic dose remains a challenge to conclude, the cannabinoid system represents a promising target for new therapeutic interventions in psychiatry.*

Conclusion: *Further controlled studies are essential to determine the precise mechanisms of action of cannabinoids on various neuropsychiatric disorders as well as the safety of their use are needed. Never just the use of 'smoking cannabis in an unlicenced way'. The use of simple 'smoked cannabis' remains dangerous because of the effects on inducing psychosis which the article itself refers to, and needs to remain illegal.*

Key words: *cannabis - cannabinoids - psychopharmacological therapeutic effects*

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INTRODUCTION

Written historical evidence reveals that CANNABIS SATIVA has been used medically, recreationally and spiritually for more than five centuries in many cultures. To this day it is considered the most-used plant-based psychoactive substance with millions of different usages across the world (Bostwick 2012). Medicines based on cannabis have been used for centuries for therapeutic purposes in many cultures. Cannabis and cannabinoids had been used in late 19th century Europe to treat pains, spasms, asthma, sleep disorders, depression and loss of appetite (Grotenhermen & Müller-Vahl 2012). The therapeutic use of cannabis has generated a lot of interest in the past years, leading to a better understanding of its mechanisms of action (Benyamina & Reynaud 2014). Cannabis-based medications have been a topic of intense study since the endogenous cannabinoid system was discovered two decades ago (Grotenhermen & Müller-Vahl 2012).

It is an indisputable fact that the abuse of cannabis and cannabinoids is increasingly widespread and is devoted much, mainly sensationalist, attention by the media. Recreational use of marijuana has not declined, despite mounting evidence of the substance's addictive potential, especially among young people, and tendency to induce and exacerbate psychological illnesses among susceptible individuals (Bostwick 2012).

Public opinion supports the medical legalization of marijuana without clear scientific evidence which would otherwise be necessary for the introduction of a new drug. Current global trends bring the idea of the legalization of marijuana to the forefront (Bostwick 2014). In 2011, for the first time, a cannabis extract "medicinal cannabis" approved for clinical use in Germany (Grotenhermen & Müller-Vahl 2012). Medicinal cannabis has received increased research attention over recent years due to loosening global regulatory changes Sarris et al. 2020).

Biological activity of cannabinoids is caused by binding to two cannabinoid receptors CB1 and CB2. Psychoactive is not only tetrahydrocannabinol (THC) but also: cannabidiol, cannabigerol or cannabichromen. Formerly, the usefulness of hemp was assessed in the relation to temporary appeasement of the symptoms of some ailments as nausea or vomiting. Present discoveries indicates that cannabis-based drugs has shown ability to alleviate of autoimmunological disorders such as: Multiple sclerosis (MS), Rheumatoid arthritis (RA) or inflammatory bowel disease (Tkaczyk et al. 2012).

More than 100 controlled clinical trials of cannabinoids or whole-plant preparations for various indications have been conducted since 1975. The findings of these trials have led to the approval of cannabis-based medicines (dronabinol, nabilone, and a cannabis extract [THC: CBD=1:1]) in several countries. In Germany, a cannabis extract was approved in 2011 for the treatment of moderate to severe refractory spasticity in multiple sclerosis. It is commonly used off label for the treatment of anorexia, nausea, and neuropathic pain. Patients can also apply for government permission to buy medicinal cannabis flowers for self-treatment under medical supervision (Grotenhermen & Müller-Vahl 2012). It should also be pointed out that cannabis and cannabinoids are effective in only a proportion of patients in possible indications such as permanent pain in multiple sclerosis or other neuropathic pain conditions or severe spasms (Wörz 2013). This contingency (that which is not necessary, but which may be, or not be, possible), which runs as theme throughout pain medicine, can therefore not offer conclusions that follow a set pattern, such as "There is now clear evidence that cannabinoids are useful for the treatment of various medical conditions," (Grotenhermen & Müller-Vahl 2012) but only conclusions along the lines that cannabinoids may be useful (Wörz 2013). Medicinal cannabis has been reported to have potential efficacy in reducing pain, muscle spasticity, chemotherapy-induced nausea and vomiting, and intractable childhood epilepsy (Sarris et al. 2020). This is correct in principle, but it does not include a definition of "conventional treatment." The rational range of indications for cannabis/cannabinoids is therefore limited (Wörz 2013).

Another studies indicates that cannabinoids play role in treatment of neurological disorders like Alzheimer disease or Amyotrophic lateral sclerosis (ALS) or even can reduce spreading of tumor cells. Cannabinoids stand out high safety profile considering acute toxicity, it is low possibility of deadly overdosing and side-effects are comprise in range of tolerated side-effects of other medications. In some countries marinol and nabilone are used as anti-vomiting and nausea drug. First cannabis-based drug containing naturally occurring cannabinoids is Sativex. Sativex is delivered in an mucosal spray for patients suffering from spasticity in MS, pain relevant with cancer and neuropathic pain of various origin. Despite the relatively low acute toxicity of cannabinoids they should be avoid in patients with psychotic disorders, pregnant or breastfeeding woman. Cannabinoids prolong a time of reaction and decrease power of concentration that's why driving any vehicles is forbidden. The most common side effects of cannabinoids are tiredness and dizziness (in more than 10% of patients), psychological effects, and dry mouth. Tolerance to these side effects nearly always develops within a short time (Grotenhermen & Müller-Vahl 2012, Žigić et al. 2021)).

Cannabis side-effects varies and depend from several factors like administrated dose, rout of administration and present state of mind. After sudden break from long-lasting use, withdrawal symptoms can appear, although they entirely disappear after a week or two (Tkaczyket al. 2012). Withdrawal symptoms are hardly ever a problem in the therapeutic setting (Grotenhermen & Müller-Vahl 2012).

Countries like the United States and Canada have modified their laws in order to make cannabinoid use legal in the medical context. It's also the case in France now, where a recent decree was issued, authorizing the prescription of medication containing "therapeutic cannabis" (decree no. 2013-473, June 5, 2013) (Benyamina & Reynaud 2014). Yet its potential application in the field of psychiatry is lesser known (Sarris et al. 2020).

To review what the studies, conducted over the past two decades, indicate about effects of the cannabis on physical and mental health as well as the impact on social functioning.

METHODS

We selected literature review using PubMed resources, to summarize the findings of the existing publications on cannabis and cannabinoids and their possible psycho-pharmacological therapeutic effects. Our main goal was to discuss only the dilemma about the question we put as the title: „Do cannabis and cannabinoids have a psychopharmacotherapeutic effect?" Due to that we presented limited data; despite there are a lot of reviews on cannabis, because we selected recent ones.

WHAT THE RESEARCHES SAY

Empirical and clinical studies conducted over the past two decades clearly indicate the harmful effects of the consumption of prepared cannabis on physical and mental health as well as the impact on social functioning (Thames et al. 2013, Gonzales et al. 2012). Generally, research supports cannabis' clear acute effect on neuro-cognition, while non-acute effects for prolonged use of marijuana are unclear and still insufficiently explored (Crane et al. 2013). Whether cannabis and cannabinoids have a psychopharmacological therapeutic effect remains unanswered. It is, therefore, important that controversies around cannabis use are discussed in order to assist medical professionals in taking the appropriate stance towards preparing Indian hemp, which is perceived by some as a poison to the mind, by others as a «rescue» medicine for the nation, and by yet another group as both the former and the latter (Tkaczyk et al. 2012). Though, longer-term studies are required to determine potential long-term adverse effects and risks of misuse and addiction (Tkaczyk et al. 2012).

The Pharmacology of Cannabis

The stereochemical structure of the active component in cannabis, trans delta 9-tetrahydrocannabinol THC dronabinol, which acts on the endocannabinoid system and binds to the CB1 receptor, was defined in 1964. Although there appear to be several endocannabinoids, only two of such endogenous mediators have been thoroughly studied so far: an endogenous ligand anandamide ("inner bliss") and 2-arachidonoylglycerol (2-AG). A general strategy seems to apply to the biosynthesis and degradation of anandamide and 2-AG, although the levels of these two compounds appear to be regulated in different, and sometimes even opposing, ways. "Endocannabinoid enzymes", that is to say enzymes that catalyse endocannabinoid biosynthesis or degradation, have been identified and in some cases cloned. The cellular and subcellular localization and the modes for the regulation of the expression and activity of these enzymes play an important role in the functions played by the endocannabinoids under physiological and pathological conditions (Devane et al. 1992, 1992a, Devane 1994, Devane & Axelrod 1994, Di Marzo 2008).

The discovery of the endogenous cannabinoid system indicated new molecules involved in various physiological processes. ESC is composed of a pair of G protein-coupled receptors that can activate low lipid mediators labeled ECBS:

- the predominantly centrally located CB1 receptor cloned in 1990 and

- the predominantly peripheral CB2 receptor cloned three years later, which expresses itself mainly on cells of the immune system (Fonseca et al. 2013, Bisogno 2008).

Many biochemical, pharmacological and psychological studies have shown that the elements of the endogenous cannabinoid system are represented throughout the body with regional variation and activity related to specific organs.

CB1 receptors were subsequently found not only in the central nervous system but also in many peripheral organs and tissues, e.g. cells of the immune system, spleen, adrenal gland, pancreas, skin, heart, blood vessels, lungs and parts of the urogenital and gastrointestinal tract (Luchicchi & Pistis 2012, Puighermanal 2012).

Activation of only CB1 and not CB2 receptors leads to the well-known cannabinoid psychotropic effect (Bostwick 2012).

Endogenous agonists of cannabinoid receptors were discovered in 1992. The two most important endocannabinoids are anandamide arahidonoyl ethanolamide and other 2- arahidonoyl glycerol, which were considered almost twins. Their pharmacological properties were initially considered to be identical (Devane et al. 1992, 1992a, Devane 1994, Devane &

Axelrod 1994, Luchicchi & Pistis 2012). Since the discovery of the endogenous cannabinoid receptor complex, it is evident that cannabinoids have an array of psychological effects. CB1 receptors and other neurotransmitters and neuromodulators in the central and peripheral nervous systems participate in a wide range of interactions (Bhattacharyya et al. 2009). For example, activation of CB1 receptors leads to retrograde neuronal inhibition of the release of acetylcholine, dopamine, GABA, histamine serotonin, glutamate, cholecystokinin, D - aspartate, glycine and noradrenaline. The CB1 receptor is the most abundant G protein receptor in the Central Nervous System (CNS) (Bhattacharyya et al. 2012).

These complex interactions explain not only the large number of psychological effects of cannabinoids but also the pharmacological effects of medicinal preparations of cannabis sativa (Bhattacharyya et al. 2009, Welty et al. 2014). Most of the effects of prepared cannabis are based on the agonistic response of THC at various cannabinoid receptors.

Some effects may be due to the activation of other receptor systems. It is assumed that the intensification of nausea and vomiting is mainly a consequence of the antagonistic actions of serotoninergic 5 hydroxytryptamine receptor (Bostwick 2012).

These studies suggest that along with the polymorphic and heterogeneous nature of the effects of cannabis, THC and CBD (cannabidiol) have different, often opposite effects on the widely distributed neural circuits that include the medio-temporal, prefrontal cortex and striatum. These brain regions are rich in cannabinoid receptors, implicating pathophysiological psychosis.

The mediotemporal, prefrontal cortex and striatum neural circuits help clarify neurocognitive mechanisms, particularly focusing on cannabis-induced acute induction of psychotic symptoms, and provide an understanding of the potential role of the CBD as an anxiolytic and antipsychotic (Bhattacharyya et al. 2012, Devinsky et al. 2014).

THERAPEUTIC POTENTIAL

Over the centuries, a number of medicinal preparations derived from *Cannabis sativa* have been employed for a variety of disorders, including gout, rheumatism, malaria, pain, and fever. These preparations were widely employed as analgesics by Western medical practitioners in the 19th century (Wörz 2013, Batalla et al. 2013). More recently, there is clinical evidence suggesting efficacy in HIV-associated neuropathic pain, as well as spasms associated with multiple sclerosis (Wörz 2013, Batalla et al. 2013). At this time, there does seem to be a growing body of basic pharmacologic data suggesting there may be a role for CBD. It is known that pharmaceutical products of

cannabis have a number of potential therapeutic effects: it can have anti-spastic, analgesic, antiemetic, anti-inflammatory and neuroprotective properties (Wörz 2013, Bhattacharyya et al. 2009, Welty et al. 2014). While on the one hand medical experts pay more attention to cannabis because of the accumulating evidence about the connection between frequent cannabis use and psychotic disorders, neuroscientists and pharmacologists have turned their attention to the potential positive effects of cannabis in neuropsychiatric disorders (Lustman et al. 2012). Conclusions concerning the neurobiological basis of adverse psychological effects or potential benefits are mainly drawn from pre-clinical studies. In light of the rapidly shifting landscape regarding the legalization of cannabis for medical and recreational purposes, it is important to highlight the significant disconnect between the scientific literature, public opinion, and related policies (Turna et al. 2017).

The constant development of neuroimaging modalities provides a unique opportunity to explore (in vivo) how different cannabinoids affect the human brain (Sagie et al. 2013, Hagmann 2013). Apart from cognitive damage, current studies investigate how marijuana affects mental illness: a high correlation between cannabis use and schizophrenia was found and a high risk to undergo a psychotic attack. Furthermore, patients with schizophrenia who used cannabis showed a selective neuro-psychological disruption, and similar cognitive deficiencies and brain morphological changes were found among healthy cannabis users and schizophrenia patients. In contrast to the negative effects of marijuana including addiction, there are the medical uses: reducing pain, anxiety and nausea, increasing appetite and an anti-inflammatory activity. Medicalization of marijuana encourages frequent use, which may elevate depression (Sagie et al. 2013).

Hagmann (2013) underlined that using a substance that has been used as a medicinal remedy for millennia to treat cancer, immunodeficiency syndrome, and muscle spasms seems an obvious thing to do. But he emphasized, that it does, however, seem completely unscientific to initiate a study of smoking cannabis in chronically ill patients because it seems to cause greater damage to the bronchi than tobacco does. It's not new for a potentially hallucinogenic plant-derived drug to have found its way into treatment, but, in Hagmann's view, more potent treatment options are available for patients with cachexia, pain, and nausea - including options gained from sufficient experience in the combination with opiates.

Furthermore, he pointed out that the problem in treating muscle spasms in underlying neurological disorders - and Grotenhermen and Müller-Vahl (2012) indirectly point this out in their table - lies in the induction of neurological adverse effects, including delirium (Hagmann 2013). To assign responsibility for the risks to the patient alone is common practice only for self-medication. It is entirely possible to remain below the hallucinogenic threshold, especially for single doses, but the pharmacodynamics cannot be reproduced without blood concentration monitoring. The article (Grotenhermen & Müller-Vahl 2012) is lacking scientific data about this. As long as these data are not available, the only option for treatment-refractory symptoms is dosage adjustment in an in-patient setting. In that scenario it seems likely that drug monitoring would be decided on, because in view of the efficacy-safety profile it seems entirely feasible that a therapeutic effect would be achieved (Hagmann 2012).

In the review of Sneider et al. (2013) of the existing Magnetic resonance spectroscopy (MRS) Magnetic resonance spectroscopic imaging (MRSI) studies of marijuana use demonstrates evidence that smoking marijuana alters brain metabolite levels, suggesting a potential neurotoxic effect of marijuana that could be related to a reduction in neuronal viability and altered inflammatory responses associated with chronic use. Future work is warranted to investigate relationships of neurochemical alterations with correlates of clinical and cognitive variables and risk-taking behaviors. Data from this limited collection of studies indicate that this is a significantly understudied area of research, warranting additional investigations, since this review was limited to only eight published studies utilizing MRS to investigate marijuana-related alterations in brain chemistry. First, studies should be conducted to characterize the effects of marijuana use using a prospective design that follows early onset users from initiation of use, through the critical period of brain development, and into the early 20s, i.e., neurobiological adulthood, when adolescent maturational changes begin to plateau. Second, future studies should specifically target marijuana use in females, in order to address potential sex-specific differences in the neurochemical consequences of marijuana use, which could offer some insight for tailoring individual treatment plans. Third, given that duration of marijuana use has been correlated with metabolite alterations across the majority of the available MRS studies, it will be important to characterize and elucidate the effects of extended periods of marijuana exposure, as well as abstinence, on proton metabolite levels and recovery in both younger and older cohorts. Lastly, given that recent pharmacological interventions targeting the GABA system in adults offer some promise for improved recovery from marijuana dependence, a more detailed understanding of marijuana effects on this inhibitory neurotransmitter system in human subjects is needed. Thus, there are a number of future directions for research in this area, utilizing powerful non-invasive methods for assaying *in vivo* neurochemistry, which would fill critical gaps in the existing marijuana use literature (Sneider et al. 2013).

Anxiety and major psychiatric disorders

Anxiety and related disorders are the most common mental conditions affecting the North American population. Despite their established efficacy, first-line anti-depressant treatments are associated with significant side effects, leading many afflicted individuals to seek alternative treatments. Cannabis is commonly viewed as a natural alternative for a variety of medical and mental health conditions. Currently, anxiety ranks among the top (Turna et al. 2017).

After careful review of the extant treatment literature, Turna, Patterson & Van Ameringen (2017) found that. The anxiolytic effects of cannabis in clinical populations are surprisingly not well-documented. The effects of cannabis on anxiety and mood symptoms have been examined in healthy populations and in several small studies of synthetic cannabinoid agents but there are currently no studies which have examined the effects of the cannabis plant on anxiety and related disorders. More high-quality clinical trials must be published before sound conclusions regarding the efficacy of cannabis for treating anxiety can be drawn (Van Amering et al. 2020).

There is scarce evidence to suggest that cannabinoids improve depressive disorders and symptoms, anxiety disorders, attention-deficit hyperactivity disorder, Tourette syndrome, post-traumatic stress disorder, or psychosis. There is very low quality evidence that pharmaceutical THC (with or without CBD) leads to a small improvement in symptoms of anxiety among individuals with other medical conditions. There remains insufficient evidence to provide guidance on the use of cannabinoids for treating mental disorders within a regulatory framework. Further high-quality studies directly examining the effect of cannabinoids on treating mental disorders are needed (Black et al. 2019).

Sarris et al. (2020) had conducted the first clinically-focused systematic review on the emerging medical application of cannabis across all major psychiatric disorders. They had discussed the current evidence regarding whole plant formulations and plant-derived cannabinoid isolates in mood, anxiety, sleep, psychotic disorders and attention deficit/hyperactivity disorder (ADHD). They found that the present evidence in the emerging field of cannabinoid therapeutics in psychiatry is nascent, and thereby it is currently premature to recommend cannabinoid-based interventions. There are some isolated positive studies which did show, revealed tentative support for cannabinoids (namely cannabidiol; CBD) for reducing social anxiety; with mixed (mainly positive) evidence for adjunctive use in schizophrenia. Case studies suggest that medicinal cannabis may be beneficial for improving sleep and post-traumatic stress disorder, however evidence is currently weak. On the other hand the preliminary research findings indicate no benefit for depression from high delta-9 tetrahydro-cannabinol (THC) therapeutics, or for CBD in mania. Only one isolated study indicates some potential efficacy for an oral cannabinoid/terpene combination in ADHD. Clinical prescriptive consideration involves caution in the use of high-THC formulations (avoidance in youth, and in people with anxiety or psychotic disorders), gradual titration, regular assessment, and caution in cardiovascular and respiratory disorders, pregnancy and breast-feeding (Sarris et al. 2020).

McLoughlin et al. (2014) in their systematic review wanted to assess the effects of cannabinoids (cannabis related chemical compounds derived from cannabis or manufactured) for symptom reduction in people with schizophrenia. They found that results are limited and inconclusive due to the small number and size of randomised controlled trials available and quality of data reporting within these trials. More research is needed to assess the effectiveness of cannabidiol in treating schizophrenia. Currently evidence is insufficient to show cannabidiol has an antipsychotic effect.

Insomnia

Like alcohol, cannabis may improve subjective sleep complaints, particularly when used over short periods of time (Angarita et al. 2016). Preliminary research into cannabis and insomnia suggests that cannabidiol (CBD) may have therapeutic potential for the treatment of insomnia. Delta-9 tetrahydrocannabinol (THC) may decrease sleep latency but could impair sleep quality long-term. CBD may hold promise for REM sleep behavior disorder and excessive daytime sleepiness, while nabilone may reduce nightmares associated with PTSD and may improve sleep among patients with chronic pain (Babson et al. 2017)

However, like alcohol, chronic cannabis use is associated with negative subjective effects on sleep that are manifested most prominently during withdrawal. However, the sleep-promoting effect of cannabis is lessened in the chronic user compared to naïve users (Chait & Zacny 1992, Chait & Perry 1994), while the negative effects of cannabis on sleep intensify with chronic use as noted above. This heavier use of cannabis may be necessary to receive its subjective sleep-promoting effects in the chronic user, but at the same time this increased use contributes to worsening overall sleep and therefore leads to continued and greater use (Angarita et al. 2016).

CANNABIS USE AND NEUROPSYCHO-LOGICAL DECLINE - EMOTIONAL AND COGNITIVE DEFICITS

Meier et al. (2012) in their study tested the association between persistent cannabis use and neuropsychological decline and determine whether decline is concentrated among adolescent-onset cannabis users. Participants were members of the Dunedin Study, a prospective study of a birth cohort of 1,037 individuals

followed from birth (1972/1973) to age 38 y. Cannabis use was ascertained in interviews at ages 18, 21, 26, 32, and 38 y. Neuropsychological testing was conducted at age 13 y, before initiation of cannabis use, and again at age 38 y, after a pattern of persistent cannabis use had developed. Persistent cannabis use was associated with neuropsychological decline broadly across domains of functioning, even after controlling for years of education. Informants also reported noticing more cognitive problems for persistent cannabis users. Impairment was concentrated among adolescent-onset cannabis users, with more persistent use associated with greater decline. Further, cessation of cannabis use did not fully restore neuropsychological functioning among adolescent-onset cannabis users. Findings are suggestive of a neurotoxic effect of cannabis on the adolescent brain and highlight the importance of prevention and policy efforts targeting adolescents (Meier et al 2012).

It has been demonstrated that cannabinoids have high biological activity and, due to their short-term and long-term effects, can cause emotional and cognitive deficits (Batalla et al. 2013). Studies show that short-term effects on processes such as short-term memory and verbal learning are reversible. Long-term effects such as cognitive impairment depend on several variables, including, primarily, the differences among marijuana users, the frequency of use, the dose and endogenous brain compensation (Meier et al. 2012, Clark et al. 2011).

In addition to research on cognitive impairment, there is increasing research on the effect of cannabis and cannabinoids on mental disorders. Using cannabis can induce schizophrenic psychosis in susceptible individuals. Previous studies show that the use of marijuana doubles the risk of schizophrenia in adolescents. Therefore, the treatment of cannabinoid drugs is contraindicated for psychosis, although the two studies demonstrated a positive effect of THC in the treatment of refractory schizophrenia (Kucerova et al. 2014). In their point view article, Damjanović et al. (2015) concluded that reviewed studies clearly suggest that cannabis abuse predicts an increased risk for schizophrenia, particularly in young adults. In addition, they underline the need to look at the problem taking into account two perspectives. On one hand, there is a need to create adequate measures to prevent the onset disease in the young at risk. Secondly, if the disorder is already present, how are we to prevent those who bear it to relapse? The issues are undoubtedly to be addressed by the health care system in general, using the basic concept of prevention – education, targeting the young and underlying possible consequences of the cannabis abuse (addiction, academic decline, social isolation, depression, and psychosis). The cannabis abuse can precipitate the positive symptoms of schizophrenia, relapse, need for in-patient treatment, and finally unfavourable outcome of the disease. Those who have already developed psychosis are not to be ignored in

psycho-education, by any of the involved in caregiving. Particular attention is to be devoted to encouraging the young presenting with psychotic symptoms to discontinue or, at the very least, reduce the frequency of the cannabis (ab)use (Damjanovic et al. 2015).

The debate continues on whether consuming high doses has long-term effects on an individual's cognitive state. According to current data, only extremely high doses of consumption which are never used for therapeutic purposes lead to irreversible cognitive impairment (Cerdá et al. 2012, Crippa et al. 2012).

The risk is much higher in children and adolescents (especially before puberty) because previous studies on the safety and therapeutic efficacy of cannabis use among individuals younger than 18 years were inadequate and incomplete (Benyamina & Reynaud 2014, Cerdá et al. 2012). However, longer-term studies are required to determine potential long-term adverse effects and risks of misuse and addiction (Benyamina & Reynaud 2014).

CONCLUSIONS

There is currently encouraging, albeit embryonic, evidence for medicinal cannabis in the treatment of a range of psychiatric disorders. Supportive findings are emerging for some key isolates. The fact that the results of previous studies establish the claim of CBD as an antipsychotic and anxiolytic, makes the above developments even more likely.

As exhibited, cannabinoids may in the future become an important option in the treatment of psychiatric symptoms and disorders. Due to CBD's safety and tolerability, the absence of psychoactive or cognitive effects, the existence of clinical trials with positive results and its broad pharmacological spectrum, CBD is a cannabinoid whose initial results will likely lead to implementation into clinical practice.

However, long-term, double-blind, placebo studies with groups of patients with different psychotic and anxiety disorders are still necessary. Further controlled studies are essential to determine the precise mechanisms of action of cannabinoids on various neuropsychiatric disorders as well as the safety of their use are needed. Likewise, due to CBD's biphasic effects, determining an adequate therapeutic dose remains a challenge, clinicians need to be mindful of a range of prescriptive and occupational safety considerations, especially if initiating higher dose THC formulas.

Thought, the cannabinoid system represents a promising target for new therapeutic interventions in psychiatry, but the rational range of indications for cannabis/cannabinoids is limited.

There remains insufficient evidence to provide guidance on the use of cannabinoids for treating mental disorders within a regulatory framework. Further high-quality studies directly examining the effect of cannabinoids on treating mental disorders are needed.

Despite the relatively low acute toxicity of cannabinoids they should be avoid in patients with psychotic disorders, pregnant or breastfeeding woman. Cannabinoids prolong a time of reaction and decrease power of concentration that's why driving any vehicles is forbidden.

Finally, it needs to be clear that any use of cannabis products would be a purified product of one specific component with proven therapeutic effects and proven safety. Never just the use of 'smoking cannabis in an unlicensed way'. The use of simple 'smoked cannabis' remains dangerous because of the effects on inducing psychosis which the article itself refers to, and needs to remain illegal.

Contribution of individual authors:

Izet Pajević: 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.

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

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

Leila Avdić: made substantial contributions to collecting data and literature searches, participated in revising the manuscript and gave final approval of the version to be submitted.

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