

Adverse effects of cannabinoid use: what is the safety paradigm?

Efeitos adversos do uso dos canabinoides: qual o paradigma de segurança?

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ABSTRACT

BACKGROUND AND OBJECTIVES: Interest in the use of marijuana (*Cannabis sativa*) for medicinal purposes has increased exponentially in recent decades, and the plant and its derivatives are becoming more frequently found in prescriptions for patients with chronic pain. All prescription drugs and illicit substances have adverse effects, even those from plants, fruits, and flowers, as has been well established with the use of tobacco, alcohol, and opium. Marijuana is no exception. The purpose of this study was to review and synthesize the evidence related to the adverse effects promoted by plant-derived cannabinoids, and the implications for the safety of using these substances in pain patients.

CONTENTS: A narrative review was conducted based on articles published in scientific journals indexed in Pubmed and Scielo between the years 2000 and 2022.

CONCLUSION: The evidence is still contradictory and weak on many aspects of adverse effects and clearly there is a need for further research and advances towards a more detailed elucidation of these effects for both non-medical and medical cannabis use. Screening and monitoring of such use, identifying situations of vulnerability to mental illness and dependence, with careful surveillance for adverse effects, is critical.

Keywords: Cannabis, Drug-related side effects and adverse reactions, Medical marijuana.

RESUMO

JUSTIFICATIVA E OBJETIVOS: O interesse na utilização da maconha (*Cannabis sativa*) com fins medicinais aumentou de forma exponencial nas últimas décadas e a planta e seus derivados vêm se tornando mais frequentemente encontrados nas prescrições médicas de pacientes com dor crônica. Todos os fármacos prescritos e substâncias ilícitas têm efeitos adversos, mesmo aquelas provenientes de plantas, frutas e flores, como já ficou bem estabelecido com o uso do tabaco, álcool e ópio. A maconha não é exceção. O objetivo deste estudo foi revisar e sintetizar as evidências relacionadas aos efeitos adversos promovidos pelos canabinoides derivados da planta, e às implicações sobre a segurança do uso destas substâncias em pacientes com dor.

CONTEÚDO: Foi realizada uma revisão narrativa baseada em artigos publicados em revistas científicas indexadas no Pubmed e Scielo, entre os anos de 2000 e 2022.

CONCLUSÃO: As evidências ainda são contraditórias e frágeis em relação a muitos aspectos dos efeitos adversos e claramente há a necessidade de mais pesquisas e avanços para uma elucidação mais detalhada destes efeitos tanto para o uso não medicinal quanto médico de cannabis. É fundamental uma triagem e monitoramento desse uso, identificando situações de vulnerabilidade a doenças mentais e dependência, com cuidadosa vigilância de efeitos adversos.

Descritores: Cannabis, Efeitos adversos e reações adversas relacionadas a medicamentos, Maconha medicinal.

INTRODUCTION

Cannabinoids are a heterogeneous group of natural, endogenous or synthetic compounds, which are able to activate receptors that are part of the endocannabinoid system. The first compounds capable of producing clinical effects were obtained from marijuana (*cannabis sativa*), a plant from which about 60 substances classified as cannabinoids are produced, among which the most relevant is tetrahydrocannabinol (THC), but cannabidiol (CBD), cannabinol, and cannabigerol, among others, can also be found¹. Later, with the discovery of the endocannabinoid system endogenous ligands such as 2-araquidonoil glycerol (2-AG) and ethanolamine O-araquidonoil (AEA) were identified, which act on cannabinoid receptors CB1 and CB2².

Cannabis products have been used by humans since prehistoric times, due to the plant's versatile uses, such as fiber, food, and medicine, as well as its adaptability to a wide variety of habitats. The first evidence of domestication, planting, and human medicinal use dates back 10.000 years, in Japan and other parts of

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HIGHLIGHTS

- The evidence is still contradictory and weak on many aspects of adverse effects.
- Increased knowledge about the extraction, purification, and synthesis of cannabinoids, as well as the pharmacology of these substances, has shed light on the mechanisms involved in their effects.
- There are an estimated 1 million and 10 million daily (or near-daily) cannabis users in Canada and the United States, respectively, making the issue a public health priority.

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the Asian continent³. In Brazil, its use was introduced by African slaves brought by the Portuguese, and it was named “*cânhamo*”. It is not, therefore, a native plant of this country⁴. The therapeutic use of cannabis products has gained strength in Brazil and in the world, and they are now prescribed for various health problems. However, over the years, the scientific documentation of the hedonistic effects of cannabis use has started to become widespread. The non-medical use of cannabis, illicit in Brazil until now, started to be seen worldwide as a problem to be discussed, just like opium and coca, since the inclusion of the issue by the Brazilian and Egyptian representatives, in the II International Opium Conference, held in 1924, in Geneva, by the former League of Nations⁴.

Increased knowledge about the extraction, purification, and synthesis of cannabinoids, as well as the pharmacokinetics and pharmacodynamics of these substances, has shed light on the mechanisms involved in their effects.

The purpose of this study was to synthesize the evidence regarding the adverse effects promoted by cannabinoid derivatives, and the implications for the safety of using these substances in pain patients.

CONTENTS

A narrative review was conducted based on a search in Pubmed and Scielo databases, using different combinations of the keywords “*cannabinoids*”; “*cannabis*”; “*adverse effects*”; “*medicinal cannabis*”; “*cannabidiol*”, between the years 2000 and 2022.

Interest in the use of cannabis for medicinal purposes (*Cannabis sativa* L.) has increased exponentially in recent decades in several countries, and the plant is becoming more frequently found in prescriptions for patients with chronic pain. To illustrate this worldwide increase, statistics can be cited that 40% of cancer patients use cannabis for pain management in countries where access is legal, such as Canada, Germany, and Israel. However, herbal and plant-derived cannabis products are not monitored like traditional pharmaceuticals, which creates doubts and uncertainties about their true health risks to patients. Although synthetic cannabis presentations available for prescription have their contents explicit, a wide variety of plants and cannabis products contain different concentrations of THC and CBD, making the effects of exposure unpredictable⁵.

According to US data, in states that have legalized cannabis, the prevalence of daily, weekly, and monthly cannabis use was much higher than in countries where it is still illegal. Evidence shows a tendency to increased consumption among adolescents, who are a particularly vulnerable age group for the onset of psychoactive substance use⁶.

All prescribed drugs and illicit substances have adverse effects, even those from plants, fruits, and flowers, as has already been well established by the use of tobacco, alcohol, and opium. Marijuana is no exception. A scoping review of 72 systematic reviews on the effects of medical cannabis found that mild adverse effects were reported as frequent in half of the reviews included in the study, and in 36% of these, severe reactions were reported. The

authors suggest that there is a possibility that the harms may outweigh the benefits⁷.

Within the current context of the consideration of laws on cannabis use around the globe and increase of its use in various medical indications, it is of paramount importance, and a matter of public health, to provide clear and evidence-based information on the undesirable, acute and persistent effects, as well as being aware of the individuals most susceptible to complications when cannabis is used for medicinal purposes.

Acute and intoxication

Cannabis use can lead to a range of behavioral or psychological changes with clinical impact, such as anxiety, euphoria, altered motor coordination, slowness, time distortion, sensory alterations, impaired judgment, and social isolation, which occur during or shortly after cannabis use and may be related to the dose that was used, the environment and previous experiences, and the individual's expectations. The most frequently observed adverse effects are panic attacks and other forms of anxiety, mainly reported by beginners⁸.

Memory and attention are negatively impacted while impulsivity is increased. Authors have shown that acute cannabis use impaired working memory and verbal memory. A study correlating pharmacogenetics and neurocognition, in different types of cannabinoid derivative use (medicinal and non-medical), showed that working, verbal and visual memories were more impacted during acute intoxication in individuals with COMT Val allele, which is believed to be a link between cannabis and schizophrenia^{9,10}. Acute cannabis toxicity is presented both with psychiatric symptoms (relaxation, time distortion, loss of inhibitions) and through physical effects (tachycardia, conjunctival edema, impairment in cognitive tasks and short-term memory), more common with higher THC ratios¹¹.

One little-known aspect of intoxication is that involving workers who handle the plants or are exposed to them, such as growers, police officers, or forensic technicians. Immediate respiratory symptoms in direct response to exposure are most common and are marked by congestion, rhinoconjunctivitis and/or chest symptoms such as coughing, wheezing, chest tightness or shortness of breath, related to bronchial hyperresponsiveness. Skin symptoms such as urticaria (contact urticaria), angioedema, and, rarely, late symptoms resembling dermatitis are also observed. Up to 20% of affected individuals may also experience anaphylactic-type reactions. Although rare, anaphylactic reactions have been reported in sensitized individuals, associated with the ingestion of hemp seeds, which are marketed as a protein health food¹².

Psychiatric effects

Psychosis and schizophrenia

Studies have shown that regular cannabis users are twice as likely to develop psychosis, and for users with very high and frequent consumption, this likelihood increases to four times. Approximately one in four individuals with schizophrenia has a concomitant diagnosis of cannabis abuse. Overall, this use has been

shown to be associated with earlier onset of psychosis, increased symptom severity, higher relapse rates, longer hospitalizations, and poorer outcomes. Users who develop psychosis are more likely to develop the symptoms at a younger age than non-users, and are more associated with THC. An experimental study has shown that intravenous THC administration in healthy individuals can directly induce the development of psychosis subjective symptoms¹³.

Despite the association that has been observed between cannabis use and schizophrenia, there is difficulty in proving a causal relationship. However, there is evidence that cannabis use affects the brain cannabinoid receptors affected by schizophrenia, cortical maturation, and mechanisms of addiction. There appears to be an overlapping genetic susceptibility to cannabis use and the development of schizophrenia, but this statement requires further investigation^{14,15}.

Anxiety

There are not a lot of studies on cannabis and anxiety, despite hypotheses that THC may provoke anxiety symptoms through its effects on serotonin and norepinephrine. There is a shortage of data, derived from the available studies, that allows for a longitudinal analysis, and therefore the available data does not reflect the potential for reverse causality. Cannabis use alone is not sufficient for the development of long-term anxiety and is at most a minor risk factor that may act in conjunction with other factors¹⁶.

A genetic study about the effects of cannabis on anxiety symptoms in 1.424 adolescents over five years showed that cannabis use is associated with an increase in anxiety symptoms only in 5-HTTLPR gene short allele carriers, not a behavior observed in the general population¹⁷.

Depression and suicidal ideation

There is a higher prevalence of cannabis use among patients with major depressive disorder compared to the general population. However, the evidence about the effects of cannabis on symptoms of depression is mixed. Some authors have reported that cannabis may be therapeutic for patients with depression, while others have shown that the substance may exacerbate symptoms. It is assumed that cannabis can both act as an outlet for depressive symptoms and can cause an increase in blunted emotions and anhedonia^{18,19}.

There are concerns about increased suicidal ideation or suicide attempts with acute or chronic cannabis use, although there is insufficient evidence to assert causality. Review studies with meta-analysis have demonstrated an association, although the included studies do not reflect current use patterns and have samples that are not representative of the general population^{20,21}.

In a nationally representative cohort of adults aged 20 to 59 in the United States, with data collected between 2005 and 2018, a significant association between cannabis use in the past 30 days and suicidal ideation was shown. Recent use was also associated with moderate to severe depression symptom profiles. These results generate further reflection on the topic and the need for additional care in individuals using the drug²².

Personality disorder

Regarding this aspect, a study of 1.419 individuals with permanent DSM-IV diagnoses draws attention, showing that some personality disorders, such as antisocial and borderline, were strongly associated with cannabis use and abuse, indicating a possible genetic and phenotypic correlation. There should be an alert for this issue that is not always systematically addressed¹⁸.

Cardiovascular effects

A possible increased risk of cardiovascular (CV) events associated with cannabis use has been reported and generated concern. Different mechanisms have been suggested as possible causes of cannabis-related CV risk, including direct reversible cerebral vasoconstriction (a possible mechanism of stroke), increased procoagulant proteins, ischemia by modulation of cannabinoid receptors in vascular smooth muscle and human cardiomyocytes, and arrhythmia. In a systematic review of 116 case reports and 29 observational studies, the authors concluded that although data are limited, there is a suggestion that cannabis use may have negative CV consequences^{23,24}.

A study that assessed the risk of cardiovascular emergency department visits and hospitalization in 18.653 adult patients authorized to use medical cannabis in Ontario, Canada from 2014 to 2017, noted that medical cannabis authorization was associated with an increased risk of emergency department visits or hospitalization for CV events, including stroke and acute coronary syndrome²⁵.

Recent cannabis use was associated with higher odds of a history of heart attack by an American study that evaluated 4.610 individuals between the ages of 18 and 44. The magnitude of this association increased among more frequent cannabis users. The large sample size, generalizability, and detailed data on cannabis use from this cross-sectional study provide unique insight into this growing public health problem²⁶.

Effects of contaminants

The non-medical community generally considers cannabis a relatively safe drug. There are, however, significant uncertainties surrounding the prevalence and effects of toxic contaminants associated with preparations, except for when good practices are employed. In addition to various factors that affect the pharmacokinetic and pharmacodynamic profile, contaminants, such as bioactive substances, can affect the absorption, distribution, metabolism, and excretion of phytocannabinoids and therefore potentially alter their effect. There is a shortage of formal research investigating this topic. There is a small case series (n=5) describing the effects of cholinergic adulteration on cannabis preparations. The results suggest that the addition of cholinergic compounds (nicotinic agonists, muscarinic antagonists, and anti-acetylcholinesterase substances) is associated with an increase in the effects of THC, serving to highlight that coadministered substances may interact with THC and other cannabinoids in a manner that modulates both their pharmacokinetics and clinical effect. More research is needed on the pharmacological effects of contaminants, especially in countries where non-rigorously controlled formulations are used by patients²⁷.

Gastrointestinal effects

Chronic cannabis use has the potential to alter and disrupt homeostasis in the gastrointestinal tract. THC can increase food absorption and inhibit gastric motor activity via CB1 receptor activation. And despite the described antiemetic action of cannabinoids, there is the cannabinoid hyperemesis syndrome, which presents as a rare condition associated with cyclic nausea and vomiting, which can be induced by prolonged, non-medical cannabis abuse^{28,29}.

Then knowledge that agonism in cannabinoid receptors may possibly influence gastrointestinal motility has made the endocannabinoid system a new target for the treatment of some diseases, such as ulcerative colitis and Crohn's disease. It is worth mentioning that a major limitation for these therapies targeting the gastrointestinal tract with the use of cannabinoids are their potential adverse effects, which cannot be neglected²⁸.

Effects on the respiratory system

The possibility that smoking cannabis may have a negative effect on the respiratory system has generated an increased focus for this issue in recent years, considering also that smoking is one of the respiratory diseases cardinal points.

There is already consistent clinical evidence between the association of smoked cannabis with increased airway inflammation, which is similar to the impact of tobacco. From clinical studies it has been observed that cannabis smokers have higher percentages of chronic bronchitis symptoms, such as cough, bronchospasm, hyperinflation, and sputum production, when compared to tobacco users³⁰.

Effects on the immune system

Cannabis use was associated with statistically significant reductions in CD4 and CD8 T cells in individuals with and without acquired immunodeficiency syndrome (AIDS), yet cannabis exposure was not associated with an increased risk of progression to AIDS or increased oral HPV infection in patients with and without HIV. It is important to highlight that individuals who use cannabis daily have more severe symptoms of HIV infection and more adverse drug effects than users who use the substance less frequently^{31,32}.

Cancer

Mutagenicity of cannabis has been demonstrated *in vitro* and that smoking cannabis produces carcinogenic substances such as nitrosamines and polycyclic aromatic hydrocarbons, which are similar to those produced by individuals who smoke tobacco. In addition, cannabis smoke contains immunosuppressants and a mixture of potentially mutagenic chemicals. Despite these studies, cannabis, unlike tobacco and alcohol, has not yet been established as a risk factor for head and neck cancer, despite questions that need explanation and clarification on the subject in the coming years³³.

Authors have shown increased risks with any type of cannabis use, including at the time of the survey, for testicular germ cell tumors, especially in users with more than 10 years of use, which

is worth warning for this population, as the increased risk result may be up to double³⁴.

Reproductive system

Chronic use of cannabis can cause altered reproductive system function. There is *in vivo* evidence to suggest that cannabis may negatively affect testosterone production and sperm motility in men. In animals, repeated treatment with cannabinoid agonists reduces testosterone secretion, alters sperm production and motility, and can inhibit ovulation. It appears, therefore, that long-term exposure, especially to THC, can result in infertility, most commonly observed in men^{35,36}.

Despite these reported associations between cannabis use and impaired fertility, there is currently insufficient concrete clinical evidence to comprehend the degree of risk of exposure to the substance in this specific respect. However, it is advisable that individuals avoid cannabis use when trying to conceive.

Maternal-fetal binomial injuries

In humans, cannabis use does not appear to be associated with low birth weight, premature delivery, or placental abruption. However, an increased risk of sudden infant death syndrome is reported in cases of cannabis use at conception, during pregnancy, and postnatally. In a study of postnatal growth, a dose-response relationship was found between head circumference and cannabis exposure, in which intense maternal exposure was associated with a smaller head circumference that persisted until 12 years of age^{37,38}.

CBD and other cannabinoids have been shown to cross the placental barrier and children who are exposed prenatally are more likely to experience numerous developmental changes, such as inattention, lower intelligence scores and poor academic performance. Exposure through lactation can delay developmental milestones in early childhood and affect communication early in life^{39,40}.

Addiction

Regular cannabis use can become an addiction in the same way as with other substances such as opioids or tobacco. The feeling of being "high" consequently generates the desire for repeated use and, for some users, this desire has the potential to become a disorder, with inappropriate use of the substance, especially in those who start this practice younger and those who have a higher frequency of exposure^{41,42}.

A research has shown that cannabis abuse is one of the most common addictions after cigarettes and alcohol in countries such as Australia, Canada, and the United States, although the rate of dependence is lower when compared to other drugs. However, this does not mean that it should be considered a trivial disease, because it is more prevalent in people who also abuse alcohol and other drugs. In recent years a steady increase in the number of users seeking assistance to control or quit cannabis use has been observed in several countries. This issue has to be looked at very closely in the coming years⁴¹.

In US states that have implemented new laws regulating cannabis, there is potential for addiction to increase due to increased

availability. There are an estimated 1 million and 10 million daily (or near-daily) cannabis users in Canada and the United States, respectively, making the issue a public health priority⁴³.

CONCLUSION

The understanding of cannabis use is rapidly changing, from new medical indications and legalization of use to the paradigm that it is not a harmless substance without consequences for those who use it, as is sometimes reported on the internet, on many websites and social media. Prolonged use has varied health implications, involving physical dependence and addiction, cognitive impairment, psychiatric changes, cardiovascular problems, infertility, and even cancer risk.

An important challenge is to compare the adverse effects of the non-medical use of cannabis, which is usually done by young adults who smoke cannabis, and the risks of medical use by older adults, usually by oral route. Screening and monitoring of this use is critical, identifying situations such as vulnerability to mental illness and dependence, with careful surveillance for adverse effects and doing dose titration, as well as close observation of the dose-response relationship before prescribing higher oral doses.

Literature reviews are still contradictory and weak on many aspects of adverse effects and clearly there is a need for further research and advancement for more detailed elucidation of these effects for both non-medical and medical cannabis use.

AUTHORS' CONTRIBUTIONS

João Batista Santos Garcia

Conceptualization, Methodology, Writing - Review and Editing, Supervision

José Osvaldo Barbosa Neto

Data Collection, Methodology, Writing - Review and Editing

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