

# Cannabis abuse in patients with psychiatric disorders: an update to old evidence

## Abuso de cannabis em pacientes com transtornos psiquiátricos: atualização para uma antiga evidência

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### Abstract

**Objective:** To perform an update on cannabis abuse by patients with psychiatric disorders. **Method:** A search was performed in the electronic databases Medline, The Cochrane Library Database, Lilacs, PubMed, and SciELO, using the keywords 'marijuana abuse', 'cannabis abuse', 'psychiatric disorders', and 'mental disorders'. Articles published until December 2009, dealing with cannabis abuse and dependence in association with other psychiatric disorders were included. **Results:** Cannabis abuse was found to be associated with increased risk for the onset of schizophrenia and chronic psychotic symptoms, although these findings require confirmation from additional research. Cannabis seems to be one of the drugs of choice of individuals with bipolar disorder, despite evidence that manic states can be induced by its use. Cannabis abuse also occurs frequently in individuals with anxiety disorders, but the relationship between the chronic nature of these conditions and the use of marijuana remains uncertain. In respect to depression, there is no clear evidence to date that depressive patients use cannabis as a form of self-medication. In individuals with psychiatric disorders, the use of cannabis has been associated with increased positive symptoms, additional negative symptoms in the course of illness, impaired treatment compliance, and more hospitalizations. **Conclusion:** The abuse of cannabis by patients with psychiatric disorders such as schizophrenia and mood and anxious disorders has a negative impact both in the acute and advanced stages of these conditions, although further investigation on this association is still necessary.

**Descriptors:** Cannabis; Marijuana abuse; Dependency (psychology); Mental disorders

### Resumo

**Objetivo:** Realizar uma atualização sobre o abuso de *cannabis* em pacientes com transtornos psiquiátricos. **Método:** Busca de artigos nas bases de dados eletrônicas Medline, The Cochrane Library Database, Lilacs, PubMed e SciELO, utilizando os descritores "*marijuana abuse*", "*cannabis abuse*", "*psychiatric disorders*" AND "*mental disorders*"; incluindo artigos que avaliaram ambas as exposições para abuso e dependência de *cannabis* e qualquer outro transtorno psiquiátrico. Foi considerado o período até dezembro de 2009. **Resultados:** Observou-se que o abuso frequente de *cannabis* pode aumentar o risco para o desenvolvimento de esquizofrenia e de sintomas psicóticos crônicos, embora estes achados ainda careçam de comprovação. A *cannabis* parece ser uma das drogas de escolha de portadores de transtorno afetivo bipolar, sendo que é descrito que estados maníacos podem ser induzidos pelo seu consumo. O abuso de maconha também frequentemente co-ocorre em indivíduos com transtornos ansiosos, sendo que a relação de cronicidade destas condições e o consumo de maconha ainda é incerta. Para depressão ainda não existem evidências claras que apontem que o consumo de *cannabis* ocorre como forma de automedicação. Em indivíduos com transtornos psiquiátricos, há relatos de que o uso da *cannabis* pode exacerbar sintomas positivos, somar efeitos negativos no curso do transtorno, contribuir para pior adesão ao tratamento e levar a maior número de hospitalizações. **Conclusão:** O abuso de *cannabis* em pacientes com transtornos psiquiátricos como esquizofrenia, transtornos do humor e ansiosos tem impacto negativo tanto na fase aguda quanto em fases mais avançadas destas condições, embora futuros estudos avaliando estas associações ainda sejam necessários.

**Descritores:** Cannabis; Abuso de maconha; Dependência (psicologia); Transtornos mentais

### Introduction

After the identification of  $\Delta^9$ -tetrahydrocannabinol ( $\Delta^9$ -THC) in the 1960s, the cloning of the CB<sub>1</sub> cannabinoid receptor, and

the ensuing discovery of the endocannabinoid system in the 1990s, a growing volume of studies have focused on the involvement of

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this system in psychiatric disorders such as schizophrenia, bipolar affective disorder (BAD), major depression, and anxiety.<sup>1-4</sup>

A number of epidemiological studies indicate that people with severe mental disorders are more likely to use, abuse, and depend on psychoactive substances – especially *cannabis* – as compared to the general population.<sup>4-6</sup> The rates of *cannabis* abuse have been reported to be 10.1% higher in schizophrenia, 14.5% among patients in a manic episode, 4.1% in major depression, 4.3% in panic disorder, and 2.4% in patients with phobias.<sup>1,2,4</sup>

The association between *cannabis* abuse (age at onset and quantity and duration of exposure) in patients with psychiatric disorders has been recognized as an independent risk factor for the occurrence of acute psychotic episodes, cognitive impairment, behavioral disturbances, symptom exacerbation, and negative events in the course of illness.<sup>7-9</sup> These findings are a source of new lines of investigation and should be taken into account in the organization of services for patients with comorbid diagnoses.<sup>10,11</sup> In spite of the changes occurring in mental health services,<sup>12</sup> the treatment proposals for patients with comorbid psychiatric disorders remain inconsistent and are frequently incompatible with some psychopharmacological interventions. Similarly, treatment strategies directed to specific subgroups in different assistance settings are deficient. For example, only 12% of patients with *cannabis*-related problems and other comorbidities receive treatment for both conditions in the United States of America (USA).<sup>11</sup> Empirical populational data from developing countries in this regard are scarce.<sup>4</sup>

Based on these considerations, this study was aimed at performing an update on *cannabis* abuse and dependence in patients with psychiatric disorders.

## Method

The search for articles was performed in the electronic databases Medline, The Cochrane Library Database, Lilacs, PubMed, and SciELO, using the keywords ‘marijuana abuse’, ‘*cannabis* abuse’, ‘psychiatric disorders’, and ‘mental disorders’.

The articles included investigated *cannabis* (marijuana) abuse and dependence associated with psychiatric disorders and were published until December 2009. There were no restraints in respect to the language of publication. The reference lists of the selected articles were checked in order to identify works that were not detected in the initial search.

## Results

### 1. Schizophrenia and psychoses

Epidemiological studies demonstrate a high prevalence of *cannabis* abuse in individuals with psychoses,<sup>13-15</sup> with rates of 23% for current use, 42.1% for lifetime use, and 22.5% for abuse.<sup>1</sup>

One possible explanation, based mostly on self-report evaluations, associates these high rates of *cannabis* use with self-medication attempts, according to the “dysphoria relief” model and unpleasant states in schizophrenia. Nonetheless, the epidemiological evidence available lends no support to this hypothesis.

Recent reviews reproduce the association between the use of *cannabis* and the onset of acute psychotic states reported in the 1930s.<sup>14-16</sup> The same reviews also indicate that the frequent abuse of *cannabis* can increase the risk to develop schizophrenia and chronic psychotic symptoms.<sup>2,7,15</sup> This risk has been reported as ranging between 1.2 and 2.8 (95% CI, Odds Ratio), particularly in more vulnerable individuals, with *cannabis* appearing as a risk factor for the development of chronic psychoses. These are the results of longitudinal studies that controlled for other risk factors and that investigated temporality, causality, association strength, biological vulnerability, and dose-effect relationships (dose, onset, and duration of exposure).<sup>2,7</sup> *Cannabis* abuse can, therefore, be considered as one of the elements in a causal constellation that leads to schizophrenia in adulthood.<sup>7</sup>

In schizophrenia patients, the use of *cannabis* can exacerbate psychotic symptoms (especially positive), induce relapse, worsen negative symptoms in the course of illness, and contribute to poor treatment compliance, leading to more hospitalizations.<sup>9,14,15</sup>

Impaired academic outcome (low educational and learning performance), professional skills, social functioning, and neurocognition (motivation, planning, visuospatial functions, impulsivity, attention, and hyperactivity) have been observed in individuals with psychotic disorders as well as in regular users of the drug.<sup>2</sup>

Such impairments become less likely to respond to treatment in function of the precociousness of the exposure to marijuana abuse, particularly during the phase of brain development.<sup>17</sup> This can be explained by the fact that around 16 years of age the endocannabinoid system reaches its peak in terms of receptor density;<sup>18,19</sup> hence the hypothesis that a chronic alteration in this system (i.e. decrease in the density of CB<sub>1</sub> receptors) might cause permanent neuropsychological and neurocognitive deficits.<sup>2</sup>

A possible neurobiological mechanism to explain *cannabis*-related deficits in schizophrenia patients involves the changes in the signaling and functioning of endogenous cannabinoids such as anandamide and its analogues. Another possible explanation is related to the facilitation of the mesolimbic dopaminergic system and to the involvement of other GABAergic and glutamatergic neurotransmitters.<sup>14</sup> Although many models have been proposed to explain the etiological relationship between *cannabis* abuse and psychosis, no hypothesis was able to adequately elucidate all the associations thus far. Thus, researchers have advocated for the integration of the cannabinoid system into the current etiological hypotheses of schizophrenia.<sup>2,20</sup>

### 2. Anxiety disorders

Anxiety symptoms have been regarded as one of the most frequently reported adverse reactions related to the use of marijuana.<sup>21,22</sup> These symptoms are more common among inexperienced users and people who suddenly stop use after a period of heavy daily abuse (at least six cigarettes/day).<sup>22</sup>

Acute intoxication can cause anxiety symptoms due to the impairment in cognitive functioning and to alterations in perception. Similarly, *cannabis* abstinence can cause anxiety

symptoms including panic attacks, generally occurring between the 2<sup>nd</sup> and 6<sup>th</sup> days after withdrawal and lasting from 4 to 14 days.<sup>23</sup>

The use of *cannabis* seems to contribute to the early appearance of panic attacks in vulnerable individuals. This is especially likely to happen among teenagers, in whom the continuous use may provoke anxiety symptoms regardless of genetic, individual or environmental characteristics.<sup>1,2,23</sup>

The relationship between marijuana and anxiety disorders seems to be modulated by the interaction of  $\Delta^9$ -THC with GABA, glutamate, serotonin, and noradrenalin pathways.<sup>2,23</sup> Evidence points out to the existence of an association between previously existing anxiety disorders and the use of *cannabis*. This situation contributes for the establishment of a cycle of “self-medication” and eventual worsening of pre-existing anxiety symptoms. Individuals with anxiety disorders are at a greater risk of using *cannabis* in an attempt to feel relaxed and to reduce anxiety. Paradoxically, the progressive and exaggerated use contributes to increase anxiety symptoms, possibly due to factors related to the dose of  $\Delta^9$ -THC. At last, anxiety symptoms might be predictors of increased *cannabis* use and of the development of dependence.<sup>1,23</sup>

Despite the growing understanding on the topic, doubts persist in relation to the chronicity of anxiety symptoms associated with the use of *cannabis*, since there is a lack of longitudinal studies evaluating clinical outcomes in patients with anxiety disorders using the drug.<sup>2,23</sup> Apparently, in individuals with a genetic predisposition for the development of anxiety disorders, *cannabis* can cause alterations in the endocannabinoid system that would result in persistent anxiety symptoms.<sup>23</sup>

The mechanisms through which marijuana interferes with anxiety are complex and have not been fully understood to date. Such mechanisms include, among others, interactions between  $\Delta^9$ -THC and non-cannabinoid neurotransmitters; a dose-dependent relationship with  $\Delta^9$ -THC; and the concentrations of other cannabinoids such as cannabidiol, which has anxiolytic effects.<sup>2,23</sup>

### 3. Mood disorders

*Cannabis* seems to be one of the main drugs of abuse in patients with BAD. Compared to the general population, patients with BAD are twice as likely to use marijuana in life (34% vs. 64%) and to develop manic symptoms.<sup>2</sup>

Three theories have been proposed to explain the use of marijuana by BAD patients.<sup>2</sup> The first hypothesis refers to a possible hypersensitivity to illicit substances in this population: genetically predisposed individuals would be more vulnerable to environmental, psychological, and biological risks, so that even the consumption of small quantities of these substances could be more harmful to this population. The second theory is that of “self-medication”, similar to the “theory of dysphoria relief” in schizophrenia. The use of marijuana would relieve dysphoric symptoms, subsequently evolving to *cannabis* dependence with a consequent worsening of the initial dysphoria. The third hypothesis is the “multiple factor” theory, according to which low academic performance, limited economical resources, impaired

interpersonal and social skills, social isolation, and acceptance by groups in which the use of marijuana is facilitated could be related to the emergence of the disorder.<sup>1,2,24</sup>

Thus far, few systematic investigations have been performed on the physiopathological involvement of *cannabis* with the endocannabinoid system in BAD. Some of these studies state that the manic symptom at the onset of BAD is unable to predict the future use of *cannabis* by this population.<sup>2</sup> Based on correlational studies, some authors have proposed the use of *cannabis* derivatives such as cannabidiol for the relief of manic and depressive symptoms;<sup>2</sup> however, initial evidence from animal and human research does not support the usefulness of this cannabinoid in these cases.<sup>25,26</sup>

Scientific evidence on the association between depressive states and *cannabis* abuse is scarcer.<sup>2</sup> There seems to be no increased risk for depression associated with the occasional use of marijuana,<sup>4,27</sup> but the heavy and regular use of the drug co-occurs with depression in a greater frequency than at random. Similarly to what happens in other psychiatric conditions described here, some studies suggest that the use of marijuana among patients with depressive disorders may be a form of “self-medication”, although this notion is not supported by currently available evidence.<sup>4,28</sup>

There is no evidence on the involvement of specific neurotransmitter systems in the facilitation of depressive disorders. The effects of the abuse of *cannabis* related to increased risk for depression are probably mediated more by social aspects than by characteristic physiopathological mechanisms, since the regular and early abuse of this substance might be associated with various environmental situations such as unemployment, criminality, and educational impairment.<sup>1,4</sup> Additionally, the comorbidity between depression and *cannabis* use may be underdiagnosed, since *cannabis* dependence can mimic depressive symptoms in some individuals.<sup>4</sup>

### Discussion

In general, studies on the association between *cannabis* use and mental disorders performed in the 1980s and 1990s were mostly uncertain in regard to the association of this substance with chronic psychoses (especially schizophrenia), whereas more recent evidence speaks in favor of this association,<sup>2,4,29</sup> although not in a conclusive manner. In respect to mood and anxiety disorders, the contrasting findings led to even greater uncertainty, impeding generalizations.<sup>2,23</sup>

The evidence available to date provides arguments both for *cannabis* prevention and legalization policies. Younger individuals that use *cannabis* are more vulnerable to the development of psychiatric disorders, with an increased risk for suffering the adverse consequences of the early exposure to the substance in comparison to adult users, and this may have a negative impact on their academic life and global functioning. Legalization would lead to an increased offer of the drug, exposing more people to the use of marijuana and, therefore, to its associated complications, among which are the development and worsening of psychotic disorders.<sup>30-32</sup>

People with psychiatric comorbidities constitute a group that poses great treatment challenges.<sup>11</sup> Ideally, the most effective models of treatment services should integrate the traditional psychiatric therapy for psychoses and for substance abuse, associating supervised psychopharmacotherapy, psychoeducation, cognitive-behavioral therapy, family and motivational therapy, social skills training, and group therapy with samples that are homogeneous in respect to diagnosis. In addition, the availability of therapeutic homes for unsuccessful outpatient cases is desirable.<sup>4,10,11</sup>

The development of standardized guidelines for the identification of *cannabis* abuse in psychiatric populations aimed at reducing the rates of non-detection are among the major recommendations for the clinical practice.<sup>4,11</sup>

Despite the controversies in research findings, it can be stated that researchers are only beginning to understand how marijuana can have detrimental effects in the course of the illness of some patients with psychiatric disorders, both in the acute and chronic

stages.<sup>2,33</sup> Additional topics of interest for research are alterations in the endocannabinoid system and the relationship between endocannabinoids and symptoms, as well as analyses of CB<sub>1</sub> receptor density in schizophrenia patients.<sup>2</sup>

## Conclusion

The abuse of *cannabis* by patients with psychiatric disorders such as schizophrenia and mood and anxiety disorders seems to have a negative impact both in the acute and advanced stages of these conditions.<sup>2,4,35</sup> Prevention strategies in primary care, integrated treatment efforts, and the performance of longitudinal studies should be encouraged in order to gather more evidence and improve prognosis in the short-term.

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\* Modest

\*\* Significant

\*\*\* Significant: Amounts given to the author's institution or to a colleague for research in which the author has participation, not directly to the author.

Note: UNIFESP = Universidade Federal de São Paulo; CNPq = Conselho Nacional de Desenvolvimento Científico e Tecnológico; FAPESP = Fundação de Amparo à Pesquisa do Estado de São Paulo.

For more information, see Instructions for authors.

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