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A review on the cannabinoids impacts on psychiatric disorders

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ABSTRACT

Psychiatric adverse effects of cannabis are mainly due to psychotic symptoms. In addition, it's one of the most used drugs by patients with severe mental disorders. Cannabis dependence must be treated concurrently with the mental disorder it often coexists with. Cannabis dependence is treated with motivational strategies and cognitive-behavioral techniques. These techniques have proven superior to the techniques used in control groups, despite low adherence to treatment and frequent relapses. Data from clinical trials are scarce for pharmacological interventions. Other useful drugs have been investigated for mental and addictive disorders, often with negative results; on the other hand, some drugs specifically act on cannabinoids. The most successful trials have been conducted with cannabinoid antagonists, phytocannabinoid extracts, nabilone, and dronabinol. Few clinical trials exist regarding the treatment of comorbid mental disorders. Typical antipsychotics for mania and anticonvulsants for maintenance treatment of bipolar disorder are recommended by observational studies and published case reports in these patients. In animal experiments, the cannabinoid system is suggested as a possible therapeutic target for treating depression and anxiety symptoms in patients with this dual condition. To treat psychosis and dependence, both approaches must be employed. In this population, cognitive-behavioral therapy and motivational strategies have proved effective. Despite little research on cannabis consumption, clinical cases indicate that cannabis abstinence is an important factor in the progression of psychosis and that most clinicians choose atypical antipsychotics to manage these conditions.

1. Introduction

The description of psychopathological alterations in relation to cannabis use dates back to ancient times. The Chinese Emperor Shen Neng is credited with introducing the use of cannabis for medical purposes, around 3,000 years BC. C., and it was already observed that the use of high doses could have adverse effects such as "seeing demons" or "communicating with spirits". In classical Greece, physicians such as Galen used the plant as a pain reliever, although it was noted that it could produce "meaningless conversation". In the 19th century, the works of the French doctor Moreau de Tours should be highlighted, who described its psychic effects and used cannabis intoxication as a model of mental illness. This author stated that there was no manifestation of mental illness that could not be found in the changes produced by cannabis.

More than 400 different substances have been identified in cannabis, of which about 60 chemically belong to the cannabinoid group. The first isolated cannabinoid was cannabinol and later cannabidiol, but it was observed that these were not responsible for the psychoactive effects until Δ9-tetrahydrocannabinol (THC) was characterized in 1964. Cannabidiol is more present in industrial hemp and little in plants for recreational consumption, and it is considered that it can counteract some effects of Δ9-THC, and in fact anxiolytic and antipsychotic effects have been described. Therefore, the proportion of THC and cannabidiol present in the plant may be relevant in the psychiatric consequences of cannabis use.

The prevalence of psychiatric disorders among cannabis addicts is quite remarkable, both in samples from the general population and in the Epidemiologic

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Catchment Area study, where up to 50% of mental disorders are reported among these addicts, as well as in samples of addicts in treatment , such as that of the prevalence study of dual pathology carried out in the Community of Madrid, where 66% of current mental disorders are obtained among cannabis addicts through a structured interview and up to 77% when personality disorders are included. In addition to the high frequency, the wide psychopathological variety associated with such consumption must be highlighted. The discovery of a neurotransmission system on which cannabinoids act has led to the development of multiple investigations into their physiological functions. It is a relevant system in brain development and in the regulation of fundamental functions such as appetite, energy metabolism, analgesia, motor control and various neuroendocrine and autonomic processes. But, in addition, it highlights the role of this modulatory system in the brain reward system, in emotional regulation and the response to stress. It is considered that it may be involved in the etiopathogenesis of a variety of mental disorders such as panic disorder, phobias, post-traumatic stress disorder, depression, eating disorders, psychoses and addictive disorders. Primary dysfunction of this system or secondary dysfunction due to continued cannabis use can thus favor the development of a wide spectrum of mental disorders.

2. Cannabis and associated mental disorders

There is a low percentage of cannabis addicts who request treatment for their addiction. On many occasions, the request for help coincides with the appearance of a serious mental disorder in relation to said consumption, fundamentally psychotic symptoms. The low demand for treatment is explained in part by the low perception of risk regarding consumption and, on the other hand, these do not identify with the rest of addicts who go to specialized care facilities. In a recent study, the following are identified as barriers to treatment: not knowing the treatment options, thinking that it is unnecessary, not wanting to stop using it, and avoiding the stigma associated with drug addiction treatment. The treatment must be carried out jointly for dependency and comorbid mental disorders, although we will separate the information from each of these.

3. Cannabis withdrawal and dependence

Although there are a good number of works that assess psychotherapeutic interventions for cannabis dependence, there is a considerable lack of clinical trials that investigate pharmacological interventions for dependence and comorbid mental disorders, so the information in this regard will come from non-experimental studies. Cannabis withdrawal has been a much-discussed entity and, thus, it does not appear in the DSM-IV diagnostic classification, although it will appear in the DSM-V, after the main characteristics of said syndrome have been described (Table 1). The controversy has been due to the fact that this picture is often absent or very mild due to the slow elimination of D9-THC from the body. However, the picture is described in more than 50% of heavy users or in 15% of regular users and, on some occasions, with a very florid clinic[1,2].

Table 1. Proposed criteria for cannabis withdrawal syndrome

Common symptoms	**Less common or equivocal symptoms**
Anger or aggressiveness	Shaking chills
Loss of appetite or weight	Depressed mood
Irritability	Abdominal pain
Nervousness/anxiety	Shaking
Concern	Sweating
Insomnia, including nightmares	

As we have pointed out, there are quite a few studies that investigate the efficacy of different psychotherapeutic interventions in cannabis dependence; To cite a few, we highlight those carried out by the following authors: Stephens et al.[3]; Copeland et al.[4]; Budney et al.[5]; Martin et al.[6]; Hendriks et al.[7]; Walker et al.[8] and the two most important clinical trials regarding the sample size obtained: the Marijuana Treatment Project[9] and the Cannabis Youth Treatment[10]. Likewise, there is a review of the Cochrane database on the efficacy of these treatments[11]. The main conclusions are: psychotherapeutic interventions are effective in cannabis dependence, the most studied are motivational strategies and cognitive-behavioral techniques, which were shown to be superior to control groups, although there are no data indicating the superiority of some strategies over others, neither about the duration of the necessary therapy or the predictive factors of better or worse evolution. In general, the most serious dependents will require more intense and prolonged interventions over time. Low adherence to treatment and frequent relapses are also highlighted.

Regarding pharmacological interventions for cannabis withdrawal and dependence, we have already pointed out the scarcity of data from clinical trials, much less than the existing data for other addictions. On the one hand, useful drugs have been investigated for other mental and addictive disorders and, on the other hand, drugs that act specifically on the cannabinoid system. We will make a brief review of the data available to date.

Among anxiolytics, buspirone has been studied in an open study with negative results[12]. Among the antidepressants, nefazodone (now withdrawn from the

market), bupropion, mirtazapine or fluoxetine have been investigated with equally negative results[13-15]. Regarding anticonvulsants, the results with valproate in randomized clinical trials have been negative[16], while the limited information on the use of lithium from open studies suggests a more favorable role[17, 18]. We do not know data on other anticonvulsants such as carbamazepine, oxcarbazepine, gabapentin, topiramate and pregabalin, which could be useful, as suggested by clinical experience.

The use of opiate antagonists such as naltrexone, used in opiate and alcohol dependence, has given controversial and varied results in cannabis dependence[19]. The effects of naltrexone are variable depending on its dose and exposure to cannabis, so its use cannot be recommended at present.

There are other drugs investigated in animals or in small clinical studies whose possible benefits have not been replicated, such as an antagonist of alpha-7 nicotinic receptors, atomoxetine, lofexidine or an inhibitor of the COMT enzyme.

At this time, the most positive data comes from trials with drugs that act on the cannabinoid system. Cannabidiol, which can reverse the reinforcing effects of THC, has been suggested as a potential treatment[20], nabilone, a synthetic cannabinoid agonist, has been investigated in six users[21] and, mainly, dronabinol, THC Orally administered synthetic drug, it has been considered that it could be the equivalent of methadone in the case of opiate dependence. This product has been shown to be superior to valproate and placebo in improving withdrawal symptoms and reducing cannabis use, although its possible abuse potential or possible psychotomimetic adverse effects remain to be clarified[22-24]. Another alternative is the use of cannabinoid antagonists such as rimonabant, already withdrawn from the market due to adverse psychological effects, or taranabant, which block the effects of THC and have been investigated in other addictions such as tobacco, alcohol or cocaine.

3. Treatment of mental disorders associated with cannabis use

There is a fairly widespread belief that cannabis is a "soft drug" with few harmful effects. The risk perception of the drug is very low, which favors the extension of its consumption. However, more and more is known about the detrimental psychiatric effects of regular users.

3.1. Flash back

The flashback refers to the phenomenon of reliving the experiences of intoxication without having consumed. It is a condition initially described with hallucinogens, but also observed in relation to cannabis use. It is transitory and usually does not require a specific intervention.

3.2. Delirium

Cannabis-induced delirium is also rare, possibly related to high-dose use, in older people, or with concomitant medical conditions. Treatment is similar to delirium of other etiologies.

3.3. Amotivational syndrome

The amotivational syndrome is a condition related to cannabis use that was widely disseminated after the initial description in 1968 but that is currently considered a controversial entity, and thus has been eliminated from nosology, in contrast to the opinion of many clinicians who consider that it is a characteristic and frequent condition among cannabis users. The picture is characterized by the presence of apathy, lack of motivation, disinterest in work or studies and personal care. There are various explanations for the cause of the condition, among others it should be noted that for some it would be the result of the state of chronic intoxication that would remit with the cessation of consumption, while for others it would be the manifestation of cognitive deterioration induced by consumption. After the description of the condition, multiple publications highlighted its relative frequency, its relationship with intense and prolonged consumption and improvement or remission with the cessation of consumption, which would be the main therapeutic measure. However, there were also descriptions of persistent symptoms despite abstinence, but due to the exclusion of current classifications, there are no studies on the efficacy of therapeutic measures. When we find a patient with this clinic, in addition to focusing on maintaining abstinence, the possible usefulness of antidepressant drugs, atypical antipsychotics, cognitive-behavioral guidelines, or cognitive rehabilitation measures should be explored, depending on whether affective, amotivational, or behavioral symptoms predominate. or cognitive deficits. It is essential to resume research on this entity for its better characterization and the development of therapeutic alternatives.

3.4. Mood and anxiety disorders

One of the most frequent adverse effects of cannabis intoxication is the appearance of anxiety and panic attacks. The induction of panic disorder after consumption is also described. In addition, epidemiological studies highlight the frequent coexistence of anxiety disorders with cannabis dependence. On the other hand, it is controversial whether regular cannabis use can induce depressive symptoms. The latest cohort studies suggest that it may increase the risk of these conditions. In completed suicides, a greater presence of cannabis than expected has been detected, which is why it is considered to be a risk factor for suicide. Similarly, cannabis use is highly prevalent among patients with bipolar disorder. The

induction of manic phases by cannabis use has been described, it can favor the appearance of psychotic symptoms in these conditions and increase the number of relapses.

There is no experimental evidence of the efficacy of certain drugs in these conditions in cannabis addicts. In a case series, paroxetine was reported to be equally effective in patients with panic disorder primary or secondary to cannabis use[25]. In a clinical trial comparing fluoxetine with placebo in cannabis addicts with major depression, no significant differences in efficacy were observed, possibly because both groups were markedly improved by concomitant psychotherapeutic interventions[26]. From the information from published clinical cases[27], the most relevant is to obtain abstinence from cannabis and, until new data are available, the recommendations would be the use of selective serotonin reuptake inhibitors for depressive symptoms and anxiety, atypical antipsychotics for mania and anticonvulsants for the maintenance of bipolar disorder in these patients. Interesting data come from animal experimentation suggesting that the cannabinoid system may be a therapeutic target to treat depressive and anxiety symptoms in patients with this dual pathology. Antidepressant and anxiolytic effects have been described, without reinforcing effects, with inhibitors of fatty acid amidohydrolase and monoacylglycerolipase enzymes, which metabolize endocannabinoids, with anandamide transport inhibitors, and with cannabidiol[28].

3.5. Psychosis

Prolonged use of large quantities of cannabis, especially when started at an early age, can cause so-called cannabis-induced psychosis, which is generally short-lived. However, such induced psychoses may be the initial manifestation of later schizophrenia[29]. The most harmful effect derived from cannabis use, without a doubt, is the risk of developing prolonged psychoses. A large number of cohort studies are consistent in indicating cannabis use as a risk factor for schizophrenia in vulnerable subjects. Consumption in young people can alter brain development and favor the subsequent onset of a psychotic picture. In addition, among patients with schizophrenia, such consumption favors non-compliance with treatment and worsens the prognosis.

There is a belief that cannabis use in schizophrenia is very persistent and that therapeutic interventions are ineffective, leading to therapeutic nihilism. However, although the evolution of said consumption is indeed more unfavorable than in non-psychotic addicts[30], it is described that a significant percentage abandons consumption, especially after a first psychotic episode, hence the importance of intervening on said consumption. [31]. In addition, the evolution of cannabis use will be one of the main factors that will determine that of psychosis, and if abstinence is achieved in these subjects, their subsequent course will resemble the more favorable evolution of psychotics non-consumers[32,33]. This consumption, in addition, can favor a worse response to antipsychotic treatment[34,35].

The treatment of psychosis and dependence must be combined, with the aim of attempting total abstinence for what has been previously mentioned, with greater emphasis after a first psychotic episode or after the diagnosis of cannabis-induced psychosis. Measures will have to be established to improve therapeutic adherence, one of the main difficulties in the treatment of these patients[36], with treatment supervision measures, drugs with simple dosages or long-acting injectables, and psychoeducational and motivational techniques.

Cognitive-behavioral psychotherapy and motivational strategies have been shown to be effective in this population[37]. In contrast, there are few pharmacological clinical trials. Drug use is usually an exclusion criterion for clinical trials with antipsychotics and we have few trials in this subgroup of psychotic addicts. The clinical cases highlight that abstinence from cannabis is going to be one of the most relevant factors in the evolution of psychosis and that most clinicians opt for the use of atypical antipsychotics to manage these conditions[27].

Clozapine is the antipsychotic for which more information is available from basic and clinical research, supporting its usefulness in this subgroup of addicted psychotics. In addition to its proven efficacy as an antipsychotic and for resistant psychotic symptoms, its effect on the decrease in the consumption and craving of certain drugs has been described, as it is superior in this regard to other atypical antipsychotics[38,39]. Mechanisms have been proposed: its action on the glutamatergic system[40], correcting a supposed dysfunction of the reward circuit[41] or its different affinity and dissociation speed on D238 receptors, in addition to possible modifications on cannabinoid receptors[42]. The main limitations are its side effects, which are poorly tolerated in this population, the need for hematological controls, and the possible interactions with other drugs that these addicts may consume. There are numerous publications on the rest of the antipsychotics, but most of them are of poor methodological quality.

The information can be divided into the following sections: 1) data from basic research suggest that atypical antipsychotics are superior to typical antipsychotics in correcting THC-induced disturbances; 2) studies comparing typical and atypical antipsychotics. Most are open studies consisting of the change from a typical antipsychotic to an atypical one that suggest the greater effectiveness of the atypicals; 3) open studies with atypical antipsychotics. There are

several studies with quetiapine, risperidone and olanzapine, but not with the rest of the atypical antipsychotics, without conclusive data, and 4) the studies that compare atypical antipsychotics are scarce, usually those that compare olanzapine with risperidone and that indicate a similar antipsychotic efficacy and little impact on consumption.

Drugs that act on the cannabinoid system have been investigated as antipsychotics, which could be of interest to psychotic addicts. Cannabinoid antagonists such as rimonabant, now withdrawn from the market, were investigated in two randomized clinical trials against placebo, with little efficacy[43,44], and cannabidiol presented controversial results in several case series[45] and positive data in a clinical trial against amisulpride whose results have not yet been published.

Therefore, abstinence from cannabis is clearly associated with a better prognosis for psychosis. Cognitive-behavioral therapy and motivational interviewing are the ones that have the most scientific evidence for their use in these patients. Atypical antipsychotics will be of choice to control psychotic symptoms, but with little effect on consumption. Finally, there is still not enough information available to assess the usefulness of drugs that act on the cannabinoid system for psychotic cannabis addicts.

4. Conclusion

Cannabis is one of the drugs with the most harmful psychiatric adverse effects, mainly due to the increased risk of psychotic symptoms. In addition, it is one of the most consumed drugs among patients with severe mental disorders with harmful effects for their evolution. Therefore, it is necessary to intervene on cannabis dependence concomitantly with the treatment of the mental disorder with which it frequently coexists. Psychotherapeutic interventions are effective in cannabis dependence; the most studied are motivational strategies and cognitive-behavioral techniques that have been shown to be superior to the techniques used for control groups, although low adherence to treatment and frequent relapses are common. Regarding pharmacological interventions, there is a notable paucity of data from clinical trials. On the one hand, useful drugs have been investigated for other mental and addictive disorders, generally with negative results, and, on the other hand, drugs that act specifically on the cannabinoid system. At this time, the most positive data comes from trials with drugs that act on the cannabinoid system, such as cannabinoid antagonists, cannabidiol, nabilone and, mainly, dronabinol. Regarding the treatment of comorbid mental disorders, there are also few data from clinical trials. Information from observational studies and published case reports recommends the use of selective serotonin reuptake inhibitors for depression and anxiety, atypical antipsychotics for mania, and anticonvulsants for maintenance treatment of bipolar disorder. in these patients. Interesting data come from animal experimentation suggesting that the cannabinoid system may be a therapeutic target to treat depressive and anxiety symptoms in patients with this dual pathology. Likewise, the treatment of psychosis and dependence must be combined. Cognitive-behavioral psychotherapy and motivational strategies have proven effective in this population. The clinical cases highlight that abstinence from cannabis is going to be one of the most relevant factors in the evolution of psychosis, and that most clinicians opt for the use of atypical antipsychotics for the management of these conditions, although they have few effects about consumption.

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