Anxiety disorders in adolescents following first cannabis consumption: case reports and review

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Abstract

Background: The present article aims to illustrate the overlap between anxiety disorders and a first cannabis use in adolescents. Although investigation in teenagers, comparatively to adults is sparse, the limited existent evidence showed a link between anxiety disorders and cannabis substance use.

Methods: The authors present 3 case reports illustrating this association in adolescents, followed by a systematic review targeting panic episodes triggered by cannabis use.

Results and Conclusions: Six studies examined the association between cannabis use and panic attacks. Current findings collectively suggest that cannabis use may be a risk factor for panic psychopathology in predisposed adolescents. The anxious symptoms in these cases lead to several attendances to the Emergency Department, commitment of the school attendance, and abandonment of physical activity, which is highly disabling for teens and their relatives.

Keywords: Panic Disorder, Adolescent, Substance Related Disorders, Systematic review, Cannabinoids, Marijuana abuse.
Introduction

Cannabis is among the most commonly used psychoactive substances in western societies [1, 2]. Adolescence is the period of excellence for experimentation of illicit drugs. Among them, marijuana is the most commonly used illicit substance among adolescents in the United States [3, 4]. There were an estimated 11 million cases of cannabis dependence globally in 1990 and 13 million cases in 2010. Prevalence appears to be higher in males than females, producing a male:female ratio of 1.8 (1.7-1.9) [5].

The last national Youth Risk Behavior Survey (YRBS), according to information from the Centers for Disease Control and Prevention, shows an increased percentage of 9th through 12th grade students in the United States, who used marijuana one or more times during their life and in the 30 days prior to the survey, from 2009 to 2011 (36.8% in 2009 and 39.9% in 2011 regarding consumption any time during their life, and 20.8% in 2009 and 23.1% in 2011 regarding consumption during the 30 days prior to the survey)[6].

The elucidation of the endogenous cannabinoid system has led to the question of how the psychological effects of cannabis can be mediated. The system consists of cannabinoid 1 (CB1) receptors, cannabinoid 2 (CB2) receptors, endogenous ligands, and the biochemical machinery for synthesis, re-uptake, and metabolism of the endocannabinoids. The CB1 receptor is the most abundant G-protein-coupled receptor in the mammalian brain and is expressed at high levels in the basal ganglia, cerebellum, hippocampus, and cortex, whereas the CB2 receptor is mainly detected in the periphery [7]. The cannabinoids can cause decreased turnover of acetylcholine and affect the monoamine and gamma-aminobutyric acid (GABA) neurons. GABA is the primary inhibitory neurotransmitter in the central nervous system (CNS) and changes in the GABA system have been linked to the pathophysiology of anxiety disorders. It is possible that cannabis may provoke anxiety reactions via GABA antagonism, resulting in enhanced CNS excitatory neurotransmission and brain hyperexcitability. Likewise, changes in acetylcholine turnover could influence GABA mediated CNS neuronal homeostasis [8, 9].

Movements are increasing to legalize this drug, due to several factors, like research on cannabidiol medical benefits, or the intense euphoria the drug produces along with a popular, though false impression that this is a “safe” drug. However, concerns about its health effects are also growing [2, 10]. In recent years, evidence of the etiological role of cannabis in the onset of psychotic symptoms and schizophrenia has accumulated. However, less attention has been given to the link between cannabis use and other mental health problems, such as mood and anxiety disorders [10, 11]. A link between panic attacks and cannabis use was initially suggested by the observation that cannabis use may acutely promote heightened levels of anxiety symptoms and elicit panic attacks under certain conditions or among certain individuals [12]. Subsequent studies have strengthened the hypotheses that more frequent cannabis use may be related to an increased risk of panic attacks [12].

The depersonalization (DP) – Derealization (DR) is characterized by a feeling of detachment from one’s surroundings (DR), and one’s own emotions, sensory perceptions, and sense of self (DP) [13]. In some cases, the persistence of symptoms of DP can be imputed to a specific episode of illicit drug use [13]. DP can appear during the intoxication period, or hours or days latter, following a period overwhelmed by obsessive thoughts about the possibility of brain damage or other adverse events triggered by the cannabis consumne, worries which are enhanced by the subsequent emergence of the DP-DR symptoms [13]. The symptoms appear to be Tetrahydrocannabinol (THC) dosage dependent. Literature refers that high doses of THC (>5mg of THC in an average height man) can cause intense fear and anxiety. In superior doses, panic attacks and phobic reactions may occur. These reactions are even more common in the first experience with the substance. Between 1960 and 1970, a traditional cannabis cigarette contained an average of 1-3% of THC: for each one made of 750mg of cannabis plant, the corresponding THC amount was 7 to 20 mg. Currently, however, modern cigarettes (joint) based on intensive cannabis selection and improvement in plant cultivation contain 6 to 30% THC. Therefore, the actual average THC dose of each joint varies between 75 to 225 mg, doses far superior to the ones necessary for anxious symptoms to occur [2, 8, 11, 14, 15].

The limited number of studies in teenagers showed some overlap between anxiety disorders and the use of illicit substances [3, 4, 11]. However, most studies focus on the long-term effects of marijuana smoking or on the existence of a comorbid anxiety disorder previously to consumption, and there are limited reports of the immediate consequences of the non-medical cannabis usage. The authors present three case reports that represent the large majority of cases seen in our clinical practice, namely in age presentation, typically between 15 and 17 years old, in the existence of a prior personal or familiar history of anxiety and depressive disorders, in the existence of an internal conflict related to the autonomy process from the parental figures, and also because of the distress and disability caused by symptom presentation. The cases were also selected because of the nonexistence of confounding factors like other related drug use, namely alcohol or tobacco, which were already pointed in the current literature as confounding factors for anxiety disorders triggered by cannabis use. The authors also focus on an important issue not conveniently discussed in the existent literature that is the fact that panic attacks triggered by cannabis consumption can lead to sustained abstinence. All cases were referred to a child and adolescent psychiatric unit after a thorough search of organic causality for the symptoms and a neurology consultation. Subjects reported the cannabis consumption during psychiatric evaluation.
The authors also conducted a systematic review of the state of the art in panic episodes triggered by marijuana abuse in the adolescent population. A literature review on the psychological and neurobiological effects of cannabis in the developing brain is critical to the implementation of more informed and programmed prevention strategies.

**Methods**

Clinical reports were selected for their relevance regarding the aim of this study. All cases were referred to a child and adolescent psychiatry unit because of the symptoms described. All participants gave their informed consent for case presentation and publication.

Paper selection was done as recommended by Preferred reported items for systematic reviews and meta-analysis (PRISMA) statement (Figure 1).

Studies related with panic attacks occurring after cannabis use were systematically searched in MEDLINE (PubMed, National Centre for Biotechnology Information, U.S. National Library of Medicine, Bethesda, Maryland). The search strategy included the MeSH terms for marijuana abuse, cannabinoids, and cannabis, as well as mesh terms included below in mesh term hierarchy, with keywords describing clinical outcome. From this source, as well as manual review of reference lists, we identified the potential studies for inclusion. Several papers were excluded after reading the abstracts because they: 1) did not present data related to the outcome; 2) were review articles; or 3) were not published in English.

**Results**

**Case Presentation**

**Case 1**

The first subject is a 17-year-old, male adolescent with no prior medical history but a maternal and paternal history of anxiety disorders. He was sent to a psychiatric consultation after having recurred to the emergency department with complaints of generalized paresthesias, dizziness, and marked distress. He also manifested severe anxiety with symptoms of derealization and depersonalization. The symptoms appeared after cannabis experimentation with his peers.

After this episode, he abandoned THC consumption but presented, daily, panic attacks, multiple somatization symptoms, and regressive behaviors that motivated recurrent visits to the Emergency Department in the following months.

It was prescribed a selective serotonin reuptake inhibitor, with transient recovery and posterior recurrence of the previous complaints, which motivated feelings of hopelessness. As he claimed to feel incapacitated for sports practice and attending school, an admission to an adolescent psychiatric unit was decided. He was discharged after improvement, however keeping intermittent periods of panic episodes, somatic complaints, and hypochondriacal concerns which appear to be triggered by the internal conflict centered in the autonomy process being held by this adolescent. A close follow-up was maintained in the outpatient setting until adulthood, when he was transferred to...
a adult psychiatric department, with a diagnosis of Panic Disorder.

Case 2
The second subject is a 15-year-old male adolescent, with history of tic disorder during childhood. He was seen by a child and adolescent psychiatrist in the emergency department because of a episode of extreme distress with symptoms of derealization and depersonalization. He had been experimenting cannabis for the first time, in recreational setting with his peers.

He was medicated with a benzodiazepine and sent to an adolescent psychiatric consultation. During the psychiatric interview in the emergency department, the diagnostic hypothesis of psychotic break due to cannabinoid use was hypothesized. During consultation, extreme anxiety, feelings of depersonalization and derealization, various somatic complaints and regressive behaviors were noted. The symptoms were compatible with the diagnosis of Cannabis-Induced Anxiety Disorder, which was confirmed by psychological evaluation; no evidence of psychotic break was found. This adolescent maintains follow-up since then, and is almost totally asymptomatic, nevertheless with a phobic/anxious functioning and remaining with feelings of culpability regarding the smoking episode. There were no recurrent behaviors of toxics consumption. He manifests, in periods of bigger distress, obsessive nature concerns about his sanity.

Case 3
The third subject is a 16-year-old male adolescent that was referred to an adolescent psychiatric consultation by a Neurologist because of recurrent panic attacks. He had already been seen by a pediatrician for organic causality exclusion. At observation, he presented multiple fears and hypochondriacal concerns, somatic complaints, and feeling of derealization and depersonalization, which he felt as impediments to school attendance and for sports practice and that motivated recurrent visits to the pediatric emergency department. Those feelings appeared after a first cannabis consumption within is peer group, however he has concealed this motive from his family and in multiple Pediatric and Psychiatric consultations. Regressive behaviors and feelings of guilt related to consumption were notorious. He was diagnosed with Cannabis-Induced Anxiety Disorder.

In his familiar background stands out anxious and depressive disorder in the mother with whom the teen, an only child, maintains a high dependency relationship.

He initiated regular monitoring in psychotherapeutic consultation, antidepressant medication with selective serotonin reuptake inhibitor, and has been proposed for a group of Psychodrama. Currently, presents with no need to resort to the Emergency room, with good control of panic attacks and has resumed his usual daily activities. There was no recurrence of consumption but retains much guilt for this behavior.

Literature review
Six studies examined the association between cannabis use and panic attacks (Table 1). Of the six studies, only one was a prospective study. This prospective study was the only one to examine this relationship in an adolescent population. The study reports an increased odds for the development of panic attacks and panic disorder with cannabis use. One cross-sectional survey reports a relationship between lifetime cannabis use and panic attacks. Another cross-sectional survey reports a co-occurrence of cannabis use and panic attacks in the previous 12 months before evaluation. A cross-sectional study which examined marijuana use, abuse, and dependence in relation to anxious and fearful responding to panic-relevant bodily sensations elicited by a biological challenge procedure reports that marijuana users self-reported panic attacks with the same frequency as marijuana dependent adults. Two studies report no significant association between cannabis use and panic attacks.

Discussion
The current article aims to assess if anxiety disorders can in fact be triggered by marijuana abuse in the adolescent population, since, although being an important clinical issue, literature in this specific matter is lacking, specially in the vulnerable age group which is adolescence.

Addiction develops from a complex interplay between the individual, the drug, and the environment. The initiation of first drug use is determined by interactions between social, cognitive, cultural, attitudinal, personality, and developmental factors. Family dysfunction and under or over controlling parents are some of the factors that may influence drug use during adolescence [16]. The adolescent in his search for independence, will try to establish a process in which he substitutes an affective relationship, which is felt as a potential threat to his autonomy, by a relationship of domination over an object, which assumes a substitutive function of the unbearable affective relationship [17].

In the presented cases, the symptoms revealed themselves so serious that, in one of the cases, the hypothesis of psychotic break was held. These episodic crisis lead teens to the emergency department repeatedly, with impairment of school attendance and abandonment of physical activities, which can be highly disabling for this youngsters. At the same time, these teenagers develop regressive behaviors, becoming more and more dependent from their parental figures. All the patients described seemed to present previous subclinical symptomatology and a great attachment to their maternal figure. Transgression of the rules seemed to have triggered a enormous feeling of guilt with subsequent exacerbation of dependence on the mother.

Thomas H. (1996) conducted a survey to estimate the frequency of various adverse effects of cannabis use and found that cannabis use was significantly related to panic attacks [18]. At that time, research already pointed to the assumption that such panic attacks were aversive to fur-
ther use of the drug. In 2006, Zvolensky et al. conducted a study to evaluate lifetime associations between cannabis use, abuse, and dependence and panic attacks [19]. Their results apparently showed that cannabis dependence, but not use or abuse, was significantly associated with increased risk for lifetime panic attacks. The authors stated, however, that panic attacks had a significantly earlier age of onset among cannabis users than among larger populations who do not use cannabis, and that this was independent from previous panic attack history, which could empirically mean that, in fact, cannabis use can trigger panic attacks. Van Laar et al. (2007) prospectively investigated whether cannabis use predicted the first incidence of anxiety disorders in adults and found no significant linear trends in this association [10]. However, in this particular study, it was only considered cannabis users those who used the drug more than five times, and those who used cannabis less than five times were considered non-users. This could mean that people who eventually have had a panic attack following first cannabis consumption and discontinued the drug, would be included in the non-users group, which constitutes a severe limitation to this study.

In another Zvolensky et al. study (2008), cannabis use was in fact associated with increased odds for the development of panic attacks and panic disorder [12]. This was the first study to show a relationship between these two factors in an adolescent population. Bon-Miller et al. (2009) results also showed that marijuana-dependent adults so as marijuana users have greater risk of reporting panic attacks in the postchallenge situation compared to people abusing this drug [20]. These analyses focused on new cases of panic attacks and panic disorder development, providing prospective empirical evidence of a link between cannabis use and dependence and panic attacks and panic disorder. In 2010, Zvolensky et al. examined the relationships between marijuana use and panic attacks in a large representative survey of adults in the United States [21]. They found marijuana use to be significantly associated with a lifetime and current history of panic attacks. Interestingly, no significant relationship was observed between current marijuana use and panic disorder history. The authors argue that such findings may be related to the fact that certain vulnerable subsets of marijuana users may discontinue use of the drug if they start to develop anxious apprehension about experiencing panic attacks in the future. This assumption is in line with what happened in the cases described above.

An important factor to account for is that anxiety disorders and substance abuse can have similar etiopathogenic causes. Cannabis use by patients with anxiety disorders might reflect an underlying genetic vulnerability. On the other hand, these same genetic factors may influence the risk for anxiety disorders in cannabis users, especially in males [11]. In the presented cases, although we cannot ascertain, for sure, a temporal relationship between cannabis use and the triggered symptoms, we evaluated patients after their first cannabis consumption and, even though there were reports of personal or familiar history of anxiety, there was no pattern of stressors prior to the onset of symptoms and all of the symptoms related to the panic disorder followed drug consumption.

### Table 1. Details of studies reporting on anxiety disorders elicited by cannabis use.

<table>
<thead>
<tr>
<th>First author, year</th>
<th>Sample</th>
<th>Sample size</th>
<th>Mean age of cases</th>
<th>Type of Study</th>
<th>Time frame of cannabis use</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zvolensky M.J., 2010</td>
<td>Adults</td>
<td>N=5672 (n=125 on the 12-month marijuana use)</td>
<td>45.05</td>
<td>Cross-sectional cohort survey</td>
<td>Lifetime and previous 12 months</td>
<td>Significant positive relationship between previous 12-month marijuana use and previous 12-month panic attacks.</td>
</tr>
<tr>
<td>Bonn-Miller MO, 2009</td>
<td>Adults</td>
<td>N=64 (n=30 on the marijuana users group)</td>
<td>20.97</td>
<td>Cross-sectional study</td>
<td>Lifetime and current</td>
<td>Marijuana users self-reported panic attacks with the same frequency as marijuana dependent adults.</td>
</tr>
<tr>
<td>Zvolensky MJ, 2008</td>
<td>Adolescents at t1, reassessed one year later as young adults</td>
<td>N=1709 at t1, N=1507 at t2, N=941 at t3</td>
<td>16.6 at t1</td>
<td>Prospective randomized study</td>
<td>Lifetime and current</td>
<td>Cannabis use was prospectively associated with an increased odds for the development of panic attacks and panic disorder</td>
</tr>
<tr>
<td>Zvolensky M.J., 2006</td>
<td>Adults</td>
<td>N=4745</td>
<td>42.6</td>
<td>Randomized cross-sectional survey</td>
<td>Lifetime</td>
<td>Cannabis dependence, but not use or abuse, was significantly associated with increased risk of having a lifetime history of panic attacks.</td>
</tr>
<tr>
<td>Van Laar M., 2007</td>
<td>Adults</td>
<td>N=3854</td>
<td>39</td>
<td>Longitudinal cohort study</td>
<td>Lifetime</td>
<td>No significant linear trends in the association between frequency levels of cannabis use and anxiety disorder.</td>
</tr>
<tr>
<td>Thomas H, 1996</td>
<td>Adults</td>
<td>N=197</td>
<td>27</td>
<td>Cross sectional community survey</td>
<td>Lifetime</td>
<td>Cannabis use was significantly related to panic attacks</td>
</tr>
</tbody>
</table>
Anxiety reactions and panic attacks seem to lead to aversion to the subsequent use of the toxics. The symptoms experienced is one of the reasons for abstinence by these teens, which makes them less vulnerable of becoming regular cannabis users [11]. In all the described subjects, abstinence followed anxious symptomatology and was maintained until the present day.

Strengths of this review include its focused scope, systematic search for relevant papers, and inclusion of international and large, population-based samples. Limitations include variability in how cannabis use was assessed and what was considered cannabis use, so as inclusion of studies with potential methodological weaknesses. However, given the lack of studies this area, all studies found were included. To mitigate limitations, we have highlighted studies weaknesses when appropriate. Another limitation is the fact that only one of the studies of this review included adolescents in the sample. This is a potential valuable area of research, since a more complete understanding of the clinical impact of cannabis in adolescents mental health will provide a refinement of intervention strategies on this matter.

Conclusion

The subject of anxiety disorders related with cannabinoids abuse in pediatric ages shows marked importance, not only because of the disability caused in the life of teenagers and families, but also by the challenge presented to the clinician, namely regarding the diagnostic similarities with psychotic break, many times difficult to distinguish but very important to do so since this distinction has consequences either at treatment and at prognosis levels.

Current findings collectively suggest that cannabis use may be a risk factor for panic psychopathology in predisposed adolescents. Such association points to marijuana as a trigger in the onset and course of panic attacks. More investigation is needed in order to clarify the mechanisms underlying the reasons why cannabis can trigger anxiety disorders. More longitudinal studies in pediatric populations are imperative so that we can obtain a full understanding of the environmental, social, and neurobiological factors involved in these disorders, so that effective treatment and primary prevention mechanisms can be established.

Abbreviations

CB1: Cannabinoid 1; CB2 cannabinoid 2; CNS: Central nervous system; DP: Depersonalization; DR: Derealization; GABA: Gamma-aminobutyric acid; NMDAR: N-Methyl-D-aspartate receptor; SPS: stiff person syndrome; VGKC: voltage-gated potassium channel.

Competing interests

The authors declare no conflict of interest.

References
