

Negative symptoms as key features of depression among cannabis users: a preliminary report

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Abstract. – OBJECTIVE: Cannabis use is frequent among depressed patients and may lead to the so-called “amotivational syndrome”, which combines symptoms of affective flattening and loss of emotional reactivity (i.e. the so-called “negative” symptomatology). The aim of this study was to investigate the negative symptomatology in depressed patients with concomitant cannabis use disorders (CUDs) in comparison with depressed patients without CUDs.

PATIENTS AND METHODS: Fifty-one patients with a diagnosis of Major Depressive Disorder (MDD) and concomitant CUD and fifty-one MDD patients were enrolled in the study. The 21-Item Hamilton Depression Rating Scale (HDRS) and the negative symptoms subscales of the Positive and Negative Syndrome Scale (PANSS) were used to assess depressive and negative symptomatology.

RESULTS: Patients with cannabis use disorders presented significantly more severe negative symptoms in comparison with patients without cannabis use (15.18 ± 2.25 vs 13.75 ± 2.44 ; $t_{100} = 3.25$ $p = 0.002$).

DISCUSSION: A deeper knowledge of the “negative” psychopathological profile of MDD patients who use cannabis may lead to novel etiopathogenetic models of MDD and to more appropriate treatment approaches.

Key Words:

Cannabis use disorders, Major depressive disorder, Amotivational syndrome, Negative symptoms.

range of 10-30% of the adult population¹. A link between cannabis use and psychosis has been observed in several studies: long-term cannabis use increases the risk of psychosis in individuals with certain genetic or environmental vulnerabilities including genetic liability, childhood trauma and urban upbringing². However, while extensive attention has been given to the links between cannabis use and psychotic outcomes³⁻⁵, the causal relationship with other psychiatric disorders and especially with depressive disorders still remains debated⁶⁻⁹.

In recent years concerns emerged on the rates of cannabis use associated with depression among young people in many countries¹⁰⁻¹³. Moreover, increasing occurrence of suicide provokes public health concerns over the possible contribution of cannabis use to its etiology¹⁴. Empirical literature reports that use of cannabis among the general adult population is 8%¹⁵, while cannabis use among subjects with depressive symptoms ranges from 17% to 40%¹⁵⁻¹⁷. Researchers have observed cross-sectional associations between cannabis use and a higher likelihood of depressive symptoms^{18,19}. Longitudinal studies suggested that weekly cannabis use increases the risk of depression in young adulthood^{20,21}, but there are contrasting results on the topic^{22,23}. The inconsistency of several findings across the different studies may be related to the use of different measures of cannabis use, as well as affective outcomes and inadequate consideration of confounding features. Risk factors for depression, in fact, include exposure to adverse life events, comorbidity with other psychopathological conditions (e.g. anxiety or sleep disorders, psychotic symptoms), socio-economic adversity,

Introduction

Cannabis is the most widely used illegal psychoactive substance in the world and the lifetime prevalence estimates of cannabis use are in the

substance use and problematic peer relationships^{24,25}; since these factors are also associated with cannabis use²⁶, controlling for them is important.

To summarize, it is a reasonable hypothesis that low-level cannabis use is not associated with an increased risk of affective disorders, while heavy cannabis use (at least weekly use) in adolescence can facilitate later development of major depressive disorder. From a psychopathological point of view, it is known that cannabis use may lead to the so-called “amotivational syndrome”²⁷ that combines symptoms of affective flattening and loss of emotional reactivity, largely similar to the so-called “negative” symptoms of schizophrenia²⁸. Although initially considered specific to schizophrenia, in fact, “negative” symptoms have subsequently been described as prominent features of other neurological and psychiatric disorders including depression²⁹, Parkinson’s disease³⁰, Alzheimer’s disease³¹ and epilepsy³². Despite the frequent occurrence of cannabis use among depressed patients, no studies to date have investigated the characteristics of “negative” symptoms in depressed patients with concomitant cannabis use disorders (CUDs). Given the information outlined above, the aim of the present study was to perform a dimensional description of negative symptoms in MDD patients with concomitant CUDs in comparison with MDD patients without CUDs.

Patients and Methods

Participants

The sample consisted of fifty-one unmedicated patients with a diagnosis of MDD/CUDs (37 males and 14 females aged 18 to 46 years [mean age: 28.29±8.02]) and fifty-one unmedicated patients with a diagnosis of MDD (33 males and 18 females, aged 18 to 46 years [mean age: 30.90±8.70]) referring at the A. Fiorini University Hospital of Terracina, Sapienza University of Rome, Italy.

After signing a written informed consent form, patients underwent a structured clinical interview according to the Structured Clinical Interview for DSM IV Disorders (SCID-I-IV) [33]. Patients were included if they had a diagnosis of MDD/CUDs or MDD and if they were 18 years or older. Patients were excluded for any of the following reasons: history of medical, neurologic diseases; other Axis I diagnosis; assumption of

Central Nervous System active drugs (excluding cannabis) in the two weeks before the study.

Measures

All the patients were administered the 21-Item Hamilton Depression Rating Scale (HAM-D)³⁴ and the negative symptoms subscale of the Positive and Negative Syndrome Scale (PANSS)³⁵. The HAM-D is a 21-item scale, but only the first 17 items are added to obtain the total score; single items are rated on a Likert scale, with 8 items ranging 0 (symptom is not present) to 4 (symptom is severe) and 9 items ranging 0-2. Scores are interpreted as follows: 0-7 is considered to be within normal range, 8-13 indicates mild depression, 14-18 indicates moderate depression, 19-22 indicates severe depression, and ≥23 indicates very severe depression³⁴. The PANSS is a 30-item clinician-rated symptom severity measure that was originally developed to assess three clusters symptoms of schizophrenia: positive symptoms (7 items), negative symptoms (7 items), and general psychopathology (16 items)³⁵. All items are rated on a 7-point Likert scale ranging from 1 (absent) to 7 (extreme severity). Although PANSS is widely used in schizophrenic research, it is also applied to MDD and other psychiatric patients³⁶⁻³⁹. Several studies reported good psychometric properties of PANSS⁴⁰⁻⁴² also in MDD patients³⁷. In the present study the negative symptoms subscales of PANSS were used.

Statistical Analysis

Differences between groups (MDD/CUDs vs. MDD) were analyzed with *t*-tests for dimensional variables, and one-way Fisher exact tests for 2*2 contingency tables. In order to avoid family-wise type-I errors, a formal Bonferroni correction was applied by dividing the limit of significance by the number of comparisons ($p = 0.05/5 = 0.01$). All the analyses were performed with the Statistical Package for the Social Sciences (SPSS) 19.0 for Windows (IBM Corporation, Armonk, NY, USA). $p < 0.05$ was considered statistically significant.

Results

Differences between groups (MDD/CUDs vs. MDD) are given in Table I. There were no significant differences between groups for socio-demographic variables and in depression severity.

Table 1. Bivariate analyses.

Variables	MDD patients with CUDs (N = 51)	MDD patients without CUDs (N = 51)	t-tests (DF = 100)	p
Age – M (SD)	28.29 ± 8.02	30.90 ± 8.70	-1.57	0.12
Education: 13+ years, %	80.4 %	88.2%		0.42 ^a
Men, %	72.5 %	64.7 %		0.52 ^a
HAM-D – M (SD)	25.12 ± 4.85	24.01 ± 5.29	1.12	0.27
PANSS-negative symptoms scale	15.18 ± 2.25	13.75 ± 2.44	3.25	0.002

SD = standard deviation; DF = degrees of freedom; HAM-D = Hamilton Depression Rating Scale
 PANSS = Positive and Negative Syndrome scale; MDD = Major depressive disorder; CUDs = Cannabis Use Disorders
^aFischer’s Exact Test two-tailed

Compared to patients without CUDs, MDD patients with CUDs had higher mean scores on the PANSS negative symptoms scale (15.18 ± 2.25 vs 13.75 ± 2.44; $t_{100} = 3.25$ $p = 0.002$).

Discussion

The results of the present study indicate that patients with cannabis use disorders present significantly more severe “negative” symptoms (i.e. blunted affect, emotional withdrawal, poor rapport, passive/apathetic social withdrawal, difficulty in abstract thinking, lack of spontaneity/flow of conversation, stereotyped thinking) in comparison with patients without cannabis use. These outcomes support previous findings indicating that “negative” symptoms are prominent features of depression²⁹ and indicate that depressed patients who are also cannabis users experience significantly worse emotional, affective, cognitive and social withdrawal than non-users.

Over the last two decades, cannabinoid research has progressed. A major breakthrough has been the discovery of a multifaceted endogenous cannabinoid system, a neuromodulatory system comprised of (i) cannabinoid receptors, among which the subtype 1 (CB1) is the most abundant in the brain; (ii) endogenous ligands for cannabinoid receptors, like anandamide and 2-arachidonylglycerol; (iii) a putative membrane transporter; and (iv) enzymes involved in the synthesis and inactivation of the endogenous ligands⁴³⁻⁴⁵. The CB1 receptor was initially identified as the neuronal target of $\Delta(9)$ -tetrahydrocannabinol (THC), the major psychoactive ingredient of cannabis.

Neocortical CB1 receptors are expressed mainly on γ -aminobutyric acid (GABA) interneurons,

while in the amygdala, hippocampus, basal ganglia and cerebellum they are expressed on both GABAergic and pyramidal neurons^{46,47}. The location and function of the endogenous cannabinoid system suggest that it may play a role in regulating the neuronal circuits involved in cognitive function, emotions, and activity in the mesolimbic reward contingency pathways^{48,49}. Therefore, the negative symptoms observed in MDD\CUDs patients could be attributed to the effect of $\Delta(9)$ THC on these neural pathways.

From a clinical point of view, a deeper knowledge of the “negative” psychopathological profile of MDD patients who use cannabis may lead to more appropriate treatment approaches. Medications targeting the dopaminergic system, i.e. bupropion⁵⁰ or methylphenidate⁵¹, could be useful in MDD patients with concomitant CUDs, as well as other approaches with proven efficacy on negative symptoms such as neurofeedback⁵² or brain modulation techniques^{53,54}.

Conclusion

The effect of exogenous cannabinoids on psychiatric disease is complex and largely unknown, and further research is needed. The recent spread of novel synthetic forms of cannabis^{55,56} and of cannabis-based forms of medications⁵⁷ give further relevance to this issue.

Disclosure

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