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Long Lasting Effects of Chronic Heavy Cannabis Abuse

Joannis N. Nestoros, MD, PhD,[1] Elena Vakonaki, PhD,[2] Manolis N. Tzatzarakis, PhD,[2] Athanasios Alegakis, PhD,[2] Markos D. Skondras, MD, PhD,[3] Aristidis M. Tsatsakis, PhD, DSc [2]

[1]Department of Clinical Psychology, Scientific Director, Synchronal Amphiaraia University of Crete Spin-off Company, Heraklion, Crete, Greece
[2]Laboratory of Toxicology, Medical School, University of Crete, Heraklion, Crete, Greece
[3]Former Psychiatrist of Psychiatric Hospital of Korydallos Prison, Korydallos, Athens, Greece

Background and Objectives: The purpose of this study was to evaluate the extent of short-term memory impairment and schizophrenia-like symptoms in heavy and systematic cannabis users and the association between the severity of abuse and the longevity of its persistent symptoms after refraining from such use.
Methods: A complete psychiatric examination and a psychometric evaluation were performed in 48 solely cannabis users. Additionally, head hair samples were analyzed and the detected cannabinoids levels were correlated with the psychometric findings.
Results: A total of 33.3% (n = 16) of the total examined cannabis users were currently imprisoned. The years of abuse ranged from 1 to 35 years and the median daily dose was 5.84.4 gr and 4.84.0 gr for prisoners (n = 16) and non prisoners (n = 32), respectively. A total of 39.6% of the users experienced hallucinations (mostly auditory), 54.2% experienced delusions (mostly ideas of reference and persecution), 85.4% had organic brain dysfunction in a test addressing visual-motor functioning and visual perception skills, and all users (100%) were found to have organic brain dysfunction in a test of visual memory immediate recall. The cannabinoid metabolite levels in the hair samples were consistent with the reported history of substance abuse and total grams of consumption for the participants below 35 years old ($p < .001$). Statistically elevated cannabinoids levels were observed in users with auditory hallucinations compared to users without any hallucinations ($p = .019$).
Conclusions: The existence of hallucinations, delusions, and organic brain dysfunction in heavy cannabis users seems to be associated with cannabinoid levels in hair. The continuation of persistent symptoms 3 months after the discontinuation of cannabis abuse, was a remarkable finding.
Scientific Significance: We provide evidence that chronic and heavy cannabis abuse results in long-lasting brain dysfunction in all users and in long-lasting schizophrenia-like psychotic symptoms in more than half of all users. These findings suggest a reevaluation of the current classification of cannabis as a "soft narcotic" which erroneously, therefore, is typically considered harmless. (Am J Addict 2017;26:335–342)

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Address correspondence to Professor Tsatsakis, Director of Division of Morphology, Head of Toxicology Laboratory, Medical School, University of Crete, P.O. Box 1393, Heraklion 71003, Crete, Greece. E-mail: tsatsaka@uoc.gr

INTRODUCTION

Cannabis is an annual, dioecious, flowering herb and its initial as well as continuous use, goes back in time. The main psychoactive ingredient of cannabis is delta-9-tetrahyrocannabinol (Δ^9-THC), while it also contains over 80 cannabinoids such as cannabidiol (CBD), cannabinol (CBN), cannabichromene, tetrahydrocannabivarin, and terpinoids.[1]

Because of the pharmacologic effects of many of its compounds, the possible beneficial or harmful effects of cannabis use is still a controversial issue among physicians, mental health professionals, philosophers, social scientists, and politicians. In most European countries, the use of cannabis is illegal, although there are strong supporters in these countries that demand its legalization. In many countries in Africa, Asia, and Latin America, smoking cannabis is legal and part of their culture. Moreover, in most countries of the world (including Great Britain and the USA), there is a widespread impression that cannabis is a "*soft*" narcotic. Cannabis users are treated by mental health professionals and the legal point of view for this type of "*soft*" narcotic is regarded as not such an important felony compared to other "*strong*" narcotics, like heroin and cocaine.

The two cannabinoid receptors, CB1 and CB2, belong to the super family of the G protein-coupled receptor, localized in the brain and are involved in various physiological processes including appetite, pain-sensation, mood, and memory.[2] The activation of CB1 and CB2 inhibits the release of other neurotransmitters such as gamma-aminobutyric acid (GABA) and glutamate.[3]

First Moreau de Tours, in the 19th century, noticed schizophrenia-like symptoms (paranoia, hallucinations, conceptual disorganization) and organic brain dysfunction (impairments in attention and memory) in the context of acute cannabis intoxication.[1]

The aim of the present study was to examine if the chronic and systematic cannabis users would undergo more easily schizophrenia-like symptoms such as delusions and

hallucinations and to correlate these findings with the severity and the duration of the use, as it is monitored and recorded by hair analysis data. Furthermore, we have tested for symptoms of organic brain dysfunction in this specific population of chronic and systematic solely cannabis users and again, correlated these findings with the harsh and time-dependent use, as it is recorded by hair analysis data.

MATERIALS AND METHODS

Participants

A total of 48 individuals (3 female, 45 male) who were heavy, chronic, and systematic and solely cannabis users, with a mean age of 30.2 ± 10.0 years, were included in this study from 2007 until 2009. The participants signed an informed consent form and a detailed history of drug abuse and psychiatric disorder was taken.

Moreover, the study passed the Ethics Committee of the University of Crete Medical School, the Ethics Committee of *"Synchronal Amphiaraia University of Crete Spin-off Company*" and the study design is consistent with the International Standards for Clinical Trial Registries.[4]

Sixteen of the participants (33.3%) were prisoners and were, therefore, abstinent from cannabis for a minimum of 2 months. A sub-sample of 8 from the 16 individuals that were imprisoned were re-examined by a psychiatrist after a period of 3 months, at a time at which they were also abstinent from cannabis according to their statement, as the disciplinary system in Greece does not allow analyzing urine samples collected from prisoners for research proposes. The participants, who were not in prison, were always under the influence of cannabis when examined.

The Court required a forensic examination of the participants with the question whether they justified the nine criteria of the Greek Republic for Drug Addiction (Ministerial Decree 148/2007).[5] According to this, the drug abuser must fulfill three of the nine criteria ((1) consumes substances in larger amounts or for longer periods than he had intended to; (2) he has a persistent desire or has had one or more unsuccessful efforts to reduce or control the use of the substance; (3) consumes much of his time in activities for supply or use of the substance; (4) displays a state of intoxication or withdrawal symptoms; (5) gives up or reduces important social, occupational, or recreational pursuits due to the use of the substance; (6) continues to use the substance despite being aware of a lasting or recurrent social, psychological, and physical health problem that has been caused or aggravated by its use, g. needs a significantly higher amount of substance or shows a significantly reduced effect with continued use of the same amount of drug; (7) displays withdrawal symptoms; (8) uses the substance very often in order to relieve or avoid withdrawal symptoms).

All participants fulfilled at least three of the nine criteria and were examined for psychiatric disorders and organic brain syndromes. Moreover, in all individuals hair analysis was performed in order to the estimate the impact of cannabis abuse.

Chemical and Reagents

Methanol (LC-MS grade) was purchased by Sigma-Adrich (St Louis, MO). Δ^9-THC (purity >97.0), cannabidiol, and cannabinol (purity > 98.5) were obtained from Lipomed (Hegenheimer, D-79576, Weil am Rhein, Germany).

Standard and Spiked Curves

Three stock solutions containing Δ^9-THC, cannabidiol, and cannabinol were prepared in methanol at a concentration of 100 μg/ml and stored at −20 °C. From each of these initial stock solutions, six new diluted solutions containing all three compounds were prepared at concentration levels of 0, .1, .2, .3, .4, and .6 ppm. Blank hair was collected from non-drug users (staff members of the Laboratory of Toxicology, University of Crete). The hair was determined to be drug free before the preparation of the spiked standards. The spiked hair samples were prepared by adding a known amount of drugs in 100 mg of blank hair at concentration levels of 0, .05, .1, .2, .3, .4, and .6 ng/mg.

Cannabinoids Extraction From Hair

The hair samples were washed with 2 ml of water (for a few minutes, twice) and with 2 ml of methanol (for a few seconds, twice) in an ultrasonic water bath for the removal of external contaminants. The samples were dried at 50 °C, cut in pieces (mm), weighed (100 mg), and transferred to a screw-top glass tube. Two milliliters of methanol were added and cannabinoids were extracted by incubating in an ultrasonic bath for 4 hours at 50 ± 5 °C. After the end of this step, the methanol was collected in a clean glass vial, was filtered through econofilters of .20 μm porosity (Corning, NY) and was evaporated to dryness under a gentle stream of N_2. The residue was reconstituted in 100 μl of LC-MS grade methanol and analyzed by a GC-MS.

Instrumental Method

Electron ionization mass spectrometric analysis was performed on a GC-MS QP-2010 Shimadzu system (Shimadzu, Japan) equipped with a Supelco Analytical SLB™-5 ms (Bellefonte PA) capillary column of 30 m length, .25 mm i.d, .25 μm film thickness. Pure helium (99.999%) with a column flow of 1 ml/min was used as a carrier gas. One microliters of each solution was injected into the system under splitless mode and analyzed under the following conditions: the column temperature was initially held at 140 °C for 3 minutes and raised to 320 °C at 30 °C/min where held for 6 minutes. The injector temperature was 230 °C. The interface and ion source temperatures were set at 320 °C and 220 °C, respectively. Quantitative analysis was achieved in selected ion monitoring (SIM) mode. The target ions (m/z) for each of the cannabinoids were m/z = **314**, 299 for Δ^9-THC, **231**, 246 for cannabidiol and **310**, 295 for cannabinol (in bold are the m/z ions that were used for the quantification), respectively. The retention times were 9.72, 10.07, and 10.32 minutes for cannabidiol, Δ^9-THC and cannabinol, respectively.

Psychometric Tests

Standard psychiatric evaluation was the one employed in North America Medical Schools and included the items asked at the Allan Memorial Institute of Psychiatry Psychiatric Evaluation, McGill University, Montreal. Among other items, it included detailed drug intake history, family history, history of present mental illness, past medical and psychiatric history, personal history (marital status, working record, etc.), present mental state, etc. Moreover, this evaluation included the Andreasen's scale for Positive[6] and Negative[7] Symptoms. Finally, the neuropsychological psychometric tests Bender–Gestalt test and Rey–Osterrieth complex figure test were used.

Bender Visual Motor Gestalt Test was used to evaluate visual-motor functioning and visual perception skills. Scores on the test were used to identify possible organic brain dysfunction.[8,9] Each participant was given nine figures, each on its own 3×5 cm card and was asked to copy it onto a piece of blank paper. The duration of each test was 7–10 minutes. Organic brain dysfunction was measured based on the protocol established by the above literature by counting the number of errors committed in coping each figure taking into account all nine figures.

The Rey–Osterrieth Complex Figure Test (ROCF) was used as a neuropsychological test for the evaluation of visuospatial constructional ability and visual memory.[10] For this test the examinees were asked to reproduce a complicated line drawing, first by copying it freehand (recognition), and then immediately after, they were asked to draw from memory (immediate recall).

These two tests are able to demonstrate if organic brain dysfunction is present even in cases where the typical psychiatric examination would not reveal any concentration or memory deficits. The psychometric tests were performed by a psychiatric staff, during or after the hair sampling, in a maximum 3 month period after being arrested, while a sub-sample of eight imprisoned people were re-evaluated after a 3 month period.

Measures of Severity and Cessation of Cannabis Use

Severity of cannabis use was characterized by the self-reported daily dose and the years of abuse. Another measure of the severity of the cannabis used was established in a similar way as the cigarette packs per years which were used in smokers in epidemiological studies. A grams $\times$ years measure is defined as: daily dose $\times$ 365 days/year $\times$ years of abuse as it is reported by the users. Cessation of cannabis use was considered if the participant was imprisoned.

STATISTICAL ANALYSIS

Continuous variables were expressed mainly in the form of mean $\pm$ SD although in many cases medians and quartiles were also present. Discrete variables were expressed in the form of n (n%). Association between discrete variables was examined by Pearson's chi-square or Fisher's exact's test where it was appropriate. Pearson's rho was used to measure the association between continuous and ordinal variables. Box and Whisker plots and scatterplots were used for graphical representation of data. IBM SPSS Statistics 20.0 was used for statistical analysis and data presentation.

RESULTS

The demographic data of the participants are shown in Table 1. Only 3 (6.3%) of the 48 participants were women, 16.7 % of the participants were divorced, 54.2% and 29.2% were single and married respectively, 56.3% were of Greek nationality while 39.6% had been arrested and examined in the past for possession and use of cannabis (Table 1). The mean age of the participants was 30.2 ± 10 years old. The participants were not significantly different in terms of imprisonment or not (Table 1).

Hair samples were analyzed for the presence of cannabinoids, opiates (morphine, 6-monoacetyl morphine, codeine and heroin), cocaine and its metabolite (benzoylecgonine), and amphetamines (amphetamine, MDA, methamphetamine, MDMA, MDEA, and MBDB). None of the hair sample had detectable levels of cocaine (limits of detection-quantification .001–.002 ng/mg both for benzoylecgonie and cocaine, respectively), opiates (limits detection-quantification .026–.087, .007–.022, .009–.029, and .001–.002 ng/mg for morphine, codeine, 6-monoacetyl morphine, and heroin, respectively), and amphetamines (limits detection were ranged from .03 to .05 ng/mg for amphetamines). On the other hand, all head hair samples were positive for cannabinoids (limits of detection-quantification .003–.009, .010–.033, and .015–.049 for CBD, Δ^9-THC and CBN, respectively).[11] Moreover, the total FAEE levels (fatty acid ethyl esters, biomarkers for the detection of alcohol abuse) in hair of the participants were measured and the detected FAEE levels were below 400 pg/mg which is considered low or no alcohol use.

No statistical differences ($p = .394$) were recorded between prisoners and non prisoners concerning cannabis abuse based on the self-reported daily dose of cannabis consumption (5.8 ± 4.4 and 4.8 ± 4.0 gr per day, respectively), cannabis possession ($p = .123$), or the total amount of cannabis consumption (grams $\times$ year) until sampling and examination day (26.235 ± 45.763 and 29.239 ± 33.542 gr of cannabis, $p = .260$, respectively). Statistically significant differences ($p = .011$) were observed between prisoners and non prisoners only for the total years of abuse (mean 8.8 ± 8.7 and 15.1 ± 9.2 years, respectively) (Table 1).

The psychological profile of the participants is presented in Table 2, where 39.6% of the participants reported hallucinations (including auditory 57.9%, visual 21.1%, and both auditory and visual 21.1%), 54.2 % of the abusers reported delusions, while, the majority of them reported both reference and persecution symptoms (57.7%), and 85.4% of the participants had depicted organic brain dysfunction evident in the clinical psychiatric evaluation (Table 2). A selected

TABLE 1. Participants' demographic, cannabis abuse, and possession data

	Prisoners ($N=16$)		Not imprisoned ($N=32$)		Total ($N=48$)		
	Mean (±SD)		Mean (±SD)		Mean (±SD)		p
Age	26.8 (8.7)		31.9 (10.3)		30.2 (10.0)		*.098*
	N	%	*N*	%	*N*	%	
Nationality							
Greek	3	11.1	24	88.9	27	56.3	*<.001*
Other	13	61.9	8	38.1	21	43.8	
Sex							
Male	14	31.1	31	68.9	45	93.8	*.206*
Female	2	66.7	1	33.3	3	6.3	
Marital status							
Single	8	30.8	18	69.2	26	54.2	*.184*
Married	7	50.0	7	50.0	14	29.2	
Divorced	1	12.5	7	87.5	8	16.7	
Previous psychiatric examination							
Yes	4	21.1	15	78.9	19	39.6	*.140*
No	12	41.4	17	58.6	29	60.4	
	Prisoners	Mean	SD	1st	Median	3rd	
Cannabis possession*	Yes	167.8	268.0	5.0	14.4	350.0	*.123*
	No	75.4	189.8	1.4	10.0	20.0	
Years of abuse	Yes	8.8	8.7	2.3	4.5	13.8	*.011*
	No	15.1	9.2	7.3	13.0	23.5	
Daily dose(gr)**	Yes	5.8	4.4	3.0	4.5	7.0	*.394*
	No	4.8	4.0	1.0	4.0	6.5	
Grams × years (gr)***	Yes	26.235	45.763	1.800	10.080	29.250	*.260*
	No	29.239	33.542	5.760	13.680	37.800	

*gr of cannabis possession on arrest.

**Self-reported daily dose of consumption (g/day).

***Estimated total amount (in gr) of cannabis consumed (daily dose × 365 days × years of abuse).

sample of eight imprisoned participants with detected psychiatric symptoms (two participants with hallucinations, three with delusions, and three with organic brain dysfunction) showed after 3 months, during the psychiatric re-evaluation, that symptoms were stable for all (100%) of the examined participants (Table 2).

In Fig. 1(A), the correlation between the grams × years of cannabis consumption and the total cannabinoids detected levels in hair of prisoners ($r=.798$, $p<.001$) and non prisoners ($r=.653$, $p<.001$) is presented.

The levels of total cannabinoids were also evaluated for their association with exposure factors (daily dose, duration of abuse, grams × years) separated into two major age groups (≤35 years old and >35 years old). Participants in the groups of >35 years old did not show any significant correlation between total detected cannabinoids levels in hair and daily dose ($r=.493$, $p=.087$), years of abuse ($r=.375$, $p<.207$), and grams × years ($r=.410$, $p=.164$). In contrast to the younger cannabis abusers (72.9% of the participants, aged ≤35 years old), a significant correlation was shown between total detected cannabinoids and daily dose ($r=.682$, $p<.001$), years of abuse ($r=.511$, $p=.002$), and grams × years ($r=.681$, $p<.001$) (Fig. 1B and C).

The existence of schizophrenia-like symptoms and organic brain dysfunction was correlated in all cases with higher levels of cannabinoids in contrast to those users who had no symptoms at all. Moreover, statistical significant correlations were observed between the total detected cannabinoids levels and the recorded auditory hallucinations ($p=.046$), visual hallucinations ($p=.009$), delusions of reference ($p=.008$), and delusions of persecution ($p=.026$) in the group of participants under 35 years old (Table 3).

DISCUSSION AND CONCLUSION

The heuristic value of this study was that the participants were extremely chronic and heavy cannabis abusers, who were not receiving any other narcotic substances (opiates, cocaine, and amphetamines), as it is verified by hair analysis tests. Thus, the daily dosage and systematic/chronic of solely cannabis abuse was known and recorded. Our study group is unique because clinical experience and relevant studies[12] show that most people experiencing medical and psychological problems because of their substance abuse are multiple drug abusers.

TABLE 2. Initial psychological profile of the participants and results of psychiatric re-evaluation

		N	%		N	%
Hallucinations	No	29	60.4	Auditory	11	57.9
	Yes	19	39.6	Visual	4	21.1
				Auditory & visual	4	21.1
Delusions	No	22	45.8	Reference	6	23.1
	Yes	26	54.2	Persecution	2	7.7
				Reference & persecution	15	57.7
				Reading one's thoughts	1	3.8
				Grandeur & reference & persecution	1	3.8
				Somatic & reference & grandeur & persecution	1	3.8
Organic brain dysfunction*	No	7	14.6	Decision making	2	5.0
	Yes	41	85.4	Concentration	3	7.5
				Memory	9	22.5
				Abstract thinking	3	7.5
				Memory & concentration	3	7.5
				Memory & concentration & abstract thinking	20	50
Psychiatric re-evaluation after 3 months						
		Before			After	
Hallucinations	Yes	2	100%	Yes	2	100%
Delusions	Yes	3	100%	Yes	3	100%
Organic brain dysfunction	Yes	3	100%	Yes	3	100%

*In the standard clinical psychiatric evaluation.

The complete psychiatric evaluation was carried out by an experienced neuropsychiatrist, who is well acquainted with psychosis, drug-abusers, and organic brain syndromes. Reliable and valid neuropsychological psychometric tests (Bender Visual-Motor Gestalt and Rey–Osterrieth Visual Memory Test) were applied and conclusively demonstrated the organic brain dysfunction induced from chronic and heavy cannabis abuse.

Auditory hallucinations correlated strongly ($p = .019$) with the levels of cannabinoids in hair. Paranoid ideation, hallucinations and delusions (of reference and persecution) were indistinguishable from those occurring in schizophrenia, paranoid type, and started in all cases after the onset of cannabis abuse. Delusions (representing a thought content disorder) were much more frequent than hallucinations (representing a perceptual disorder). Delusions, which by themselves justify the diagnosis of a paranoid schizophrenia-like type substance induced psychosis, were found in 26 out of the 48 heavy chronic cannabis abusers. The most, however, striking finding of our study was the memory impairment that was clearly evident in the Rey–Osterrieth Visual Memory Test in all participants in the study (100% of sample). Even the patients that were unable to perform well on the Bender Visual-Motor Gestalt test were able to draw within normal limits and copy while looking at the complex figure of the Rey–Osterrieth Visual Memory Test. However, they were very surprised when they realized how poorly they performed when they tried to draw from memory the same figure that they had completed immediately before. Additionally, it is of significant importance that the symptoms were stable after 3 months in psychiatric re-evaluation.

Moreover, the Bender Visual-Motor Gestalt test revealed organic brain dysfunction in visual- motor functioning and visual perception skills as follows: out of the 48 heavy chronic cannabis abusers, 10 (20.83%) had borderline organic brain dysfunction, 15 (31.25%) had mild brain dysfunction, 16 (33.33%) had moderate organic brain dysfunction, and 7 (14.58%) had severe organic brain dysfunction.

Our findings are in agreement with a recent extensive review of the literature on the chronic effects of cannabis on memory in humans,[13] although the methodology employed in these studies was different to our study. Moreover, a recent meta-analytical review of structural brain alterations in non-psychotic cannabis users[14] found a consistent smaller hippocampus in users as compared to non users. However, we must stress that *in our study, we demonstrated that chronic cannabis abuse in heavy doses does not only cause memory impairment. It does also cause significant brain dysfunction which involves other systems, like the visual-motor system.* Our results are consistent with the findings of Filbey[15] who measured gray matter (GM) volume via structural MRI across the whole brain and reported that, compared to controls, marijuana users had significantly less bilateral orbitofrontal gyri volume, higher functional connectivity in the orbitofrontal cortex (OFC) network, and higher structural connectivity in tracts that innervate the OFC (forceps minor) as measured by fractional anisotropy (FA). The above areas are involved in the organic brain dysfunction reflected in the Bender Visual-Motor Gestalt test. Lastly, according to the literature[16] cannabis abuse in adolescence results in lowering IQ scores in adult life, a phenomenon that persists even after cannabis discontinuation.

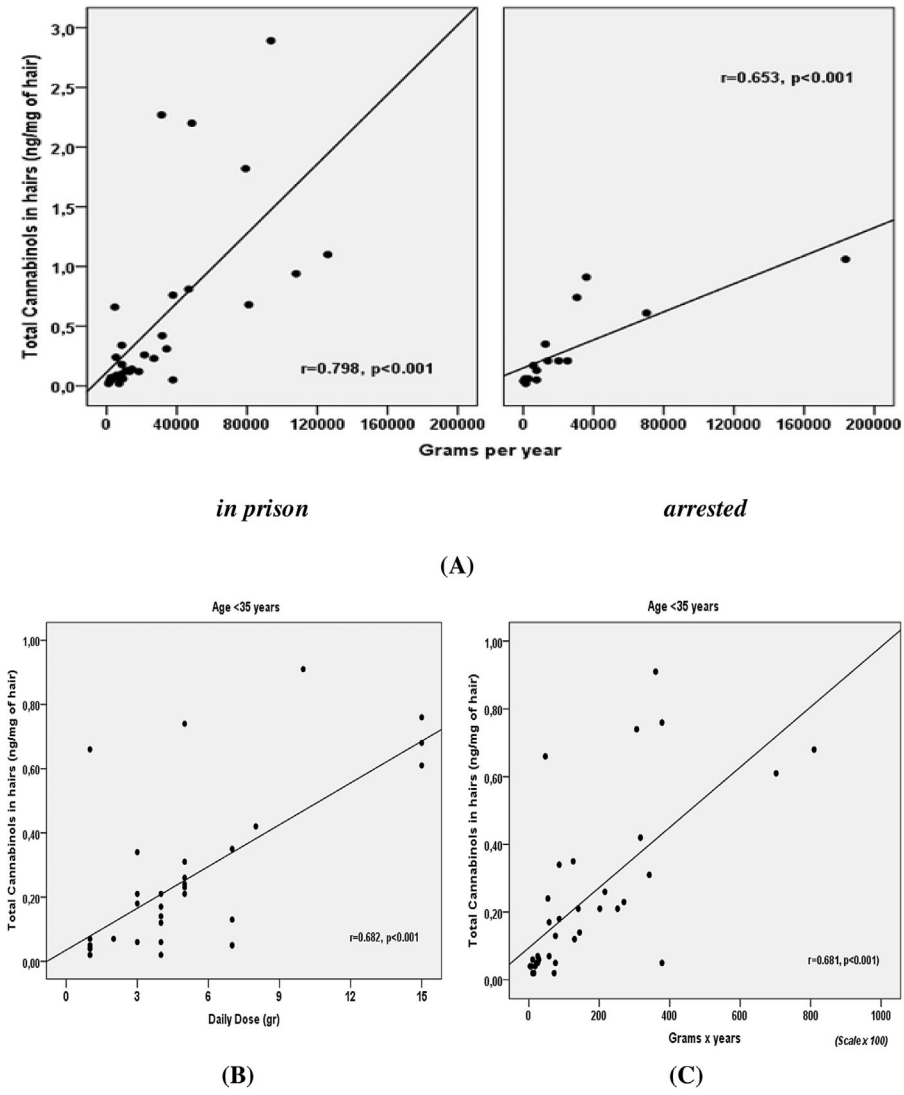

FIGURE 1. Correlation of the grams × years of cannabis consumption (scale × 100) and total cannabinoids levels in hairs of prisoners (in prison) or not prisoner, ($r = .798$, $p < .001$ (in prison), $R = .653$, $p < .001$ (arrested) (A) and the daily dose (gr) of cannabis (B) or grams × years (C) with total detected cannabinoids levels in hair of participants aged ≤35 years.

The association of cannabis use with schizophrenia is a complex issue. Firstly, it is known that individuals with schizophrenia are at a high risk for substance use disorders.[17–19] Secondly, almost 60% of patients with schizophrenia use illicit drugs.[20] Thirdly, substance use and misuse is associated with many detrimental effects on individuals with schizophrenia. Studies have shown that misuse of substances among those with schizophrenia is associated with greater severity of symptoms and poorer prognosis, significantly more admissions to hospital and outpatient visits, higher medication dose, and medication non adherence.[21–26] Rathbone and co-authors[27] in their review of the literature concluded that "*at present, there is insufficient evidence to support or refute the use of cannabis/cannabinoid compounds for people suffering with schizophrenia.*" Their "*review highlights the need for well designed, conducted and reported clinical trials to address the potential effects of cannabis based compounds for people with schizophrenia.*"

In view of the above, it is very important that from the longitudinal history of the chronic heavy cannabis abusers of our study, it is clear from the detailed psychiatric history taken that schizophrenic symptoms started in those that exhibited them at least one year after the onset of heavy cannabis abuse. This proves that cannabis intoxication, exactly like amphetamine and cocaine intoxication, may manifest itself with symptoms identical to that of the schizophrenia, paranoid type. Snyder[28] suggested that amphetamine psychosis is mediated by the catecholamines, which include dopamine, implicated in schizophrenia by the same author[29] and many others.[30–32] Serper and co-authors[33] emphasized the symptomatic overlap of cocaine intoxication and acute schizophrenia at Emergency presentation and nowadays the role of dopamine in cocaine abuse is well documented.[34] Lastly, Δ^9-tetrahydrocannabinol and other direct-acting cannabinoid agonists can induce psychotic symptoms both in healthy volunteers[35–37] and schizophrenic patients.[38,39] Moreover, it is known that

TABLE 3. The differences of cannabinoids levels in hair samples and the recorded symptoms in cannabis users

	Total cannabinoid levels in hair (ng/mg)				
	No		Yes		
	Mean	±SD	Mean	±SD	*p*
Auditory hallucinations	.32	.45	.78	.88	*.019*
Visual hallucinations	.44	.66	.57	.57	*.646*
Delusions of reference	.40	.64	.52	.66	*.538*
Delusions of persecution	.39	.59	.57	.73	*.350*
Somatic delusions	.41	.54	2.89	–	*ND*
Memory impairment	.28	.37	.54	.73	*.206*
Concentration	.41	.53	.51	.74	*.608*
Decision making	.45	.65	.61	.69	*.742*
Abstract thinking	.45	.57	.47	.73	*.910*
Organic brain dysfunction*	.30	.40	.49	.68	*.494*
Under 35 years old					
Auditory hallucinations	.19	.22	.39	.29	*.046*
Visual hallucinations	.20	.23	.50	.25	*.009*
Delusions of reference	.13	.13	.35	.29	*.008*
Delusions of persecution	.17	.18	. 36	.31	*.026*
Somatic delusions	.24	.25	–	–	*ND*
Memory impairment	.19	.22	.26	.26	*.464*
Concentration	.25	.27	.24	.24	*.853*
Decision making	.24	.25	–	–	*ND*
Abstract thinking	.25	.25	.24	.26	*.872*
Organic brain dysfunction*	.26	.36	.24	.24	*.888*

*In the standard clinical psychiatric evaluation.

cannabis abusers were subsequently in the future diagnosed as suffering from schizophrenia.[40–43] Thus, it has been hypothesized that hyperactivity of the endocannabinoid system might contribute to psychotic states,[44,45] although, we interpret the evidence as clearly implicating the agonistic stimulation of CB1 and CB2 receptors to schizophrenia-like symptoms, whereas the role of anandamide and other endocannabinoids needs further exploration. For example, as elaborated before, cannabidiol (CBD), a novel candidate antipsychotic, displays an unexpectedly high potency as an antagonist of CB1 and CB2 receptor agonists[46] while at the same time it inhibits the intracellular degradation of anandamide.[47]

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Declaration of Interest

The authors report no conflicts of interest.

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