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# Comparative Study between Effect of Cannabis and Synthetic Cannabinoids on Cognitive Functions

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**ABSTRACT**

**Background:** Synthetic cannabinoid usage is on the rise around the world, and it has become a huge global health issue. Previous studies showed a relationship between synthetic cannabinoids and cognitive function decline either after acute or chronic usage.

**Aim of the work:** The present study aims at comparing between natural and synthetic cannabinoids effect on cognitive functions in a sample of Egyptian patients.

**Patients and Methods:** Thirty patients using synthetic cannabinoids with or without cannabis and 30 patients using cannabis were included in the study. Montreal Cognitive Assessment was used to test cognitive functions.

**Result:** Impairments in attention, language, orientation, abstract thinking, visuospatial and executive functions were observed in patients using synthetic cannabinoids with or without cannabis and were significantly higher than in patients using cannabis alone.

**Conclusion:** Synthetic cannabinoids and cannabis both cause cognitive dysfunction and when cannabis abusers add synthetic cannabinoids to cannabis, it causes more cognitive dysfunction. According to the findings of this study, future research should focus on evaluating each cognitive domain with more extensive test batteries and supporting these assessments with brain imaging studies.

**Keywords:** *Synthetic Cannabinoids ; Cannabis ; Cognitive functions.*

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## INTRODUCTION

New sort of substances named Synthetic Cannabinoids (SC) have recently gained popularity between drug abusers all over the world. SCs produce more severe effects than natural cannabis. SCs are cheaper, and undetectable in usual drug tests [1]. These distinguishing characteristics leaded to the rising number of recreational drug users who abuse SCs. Synthetic cannabinoids, whether consumed once or frequently, have been associated to executive-function impairment.[1] It was found that synthetic cannabinoid abusers did significantly worse on the n-back task, the Stroop task and the long-term memory task than both recreational cannabis users and healthy individuals[2]. Synthetic cannabinoid abusers had much lower attention, memory, executive, and visuospatial abilities than people abusing cannabis alone and healthy individuals [3], this work aimed to illustrate potential impairments in cognitive functions in individuals using synthetic cannabinoids with or without cannabis and to compare the results with those from people who abuse cannabis only in a sample of Egyptian patients.

## PATIENTS AND METHODS

Participants were 60 males between 18 and 35 years old. Two groups were presented in our study: SC abusers' group (with or without cannabis) and cannabis-only abusers' group. The first was the group of SC abusers (with or without cannabis) and included 30 male patients, and the second group was cannabis-only abusers and included 30 male patients, all patients did not abuse other substances except nicotine, all patients were with education level of high school at least and were selected by consecutive sampling from patients were going to addiction outpatient clinic at Banha Psychiatric Hospital in Egypt in the period between December 2020 to August 2021.

Exclusion criteria included presence of organic mental disease, taking any medications or tonics that may affect cognition at the time of examination, Comorbid Psychiatric disorder (except Personality disorder) and any other drug abuse (except nicotine and caffeine).

We obtained The Ethics Committee approval before the study. All participants provided their informed consent.

In this research, we did Semi-Structured Psychiatric interview (for clinical diagnosis according to DSM-5) to all patients then, Urine toxicology screen for (cannabis, benzodiazepines, opiates, amphetamine, cocaine, barbiturates and tramadol) for exclusion of other substance abuse, also urine synthetic cannabinoids screen have been done to all patients after that, Montreal Cognitive Assessment (MoCA test), (for assessment of cognitive functions) has been done to all patients.

The MoCA contains 13 items to measure 7 cognitive domains:

Executive functioning; visuospatial abilities; attention, concentration; language; abstraction; memory; and orientation. In this study we used the authorized Arabic translation of MoCA version 7.1 [4]

Conducting the MoCA takes approximately fifteen minutes and scoring has been done mostly during conducting it. The aggregate of all item scores was used to produce a total score, which could be up to thirteen points, where greater scores indicate better cognitive functions, "Normal" was defined as a score of 26 or higher.[4]

The data was reorganized, coded, tallied, and converted into digital using (SPSS, version 22).

## RESULTS

| | | Group I | Group II | Test value | P-value | Sig. |
|---|---|---|---|---|---|---|
| | | No. = 30 | No. = 30 | | | |
| **Age (years)** | Mean ± SD | 22.80 ± 3.79 | 24.43 ± 5.62 | -1.320• | 0.192 | NS |
| | Range | 19 – 35 | 18 – 35 | | | |
| **Sex** | Male | 30 (100.0%) | 30 (100.0%) | – | – | – |
| | Female | 0 (0.0%) | 0 (0.0%) | | | |
| **Marriage** | Single | 24 (80.0%) | 22 (73.3%) | 0.373* | 0.542 | NS |
| | Married | 6 (20.0%) | 8 (26.7%) | | | |
| **Education** | Industrial high school | 10 (33.3%) | 14 (46.7%) | 4.952* | 0.084 | NS |
| | High school | 2 (6.7%) | 6 (20.0%) | | | |
| | Industrial diploma | 18 (60.0%) | 10 (33.3%) | | | |
| | College | 0 (0.0%) | 0 (0.0%) | | | |
| **Job** | Occupied | 28 (93.3%) | 30 (100.0%) | 2.069* | 0.150 | NS |
| | Not occupied | 2 (6.7%) | 0 (0.0%) | | | |
| **Duration of Abuse (years)** | Median (IQR) | 2 (1 – 3) | 6.5 (4 – 8) | -5.25586≠ | 0.00001 | HS |
| | Range | 1 – 5 | 1 – 20 | | | |

P-value > 0.05: Non-significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant

:*Chi-square test; •: Independent t-test; ≠: Mann-Whitney test

**Table 1:** comparison of socio-demographic data and duration of substance abuse between 2 groups.

| | | Group I | Group II | Test value | P-value | Sig. |
|---|---|---|---|---|---|---|
| | | No. = 30 | No. = 30 | | | |
| **Draw a broken line** | No | 20 (66.7%) | 19 (63.3%) | 0.073* | 0.787 | NS |
| | Yes | 10 (33.3%) | 11 (36.7%) | | | |
| **Viso-spatial Activity** | | | | | | |
| **Copying cube** | No | 24 (80.0%) | 23 (76.7%) | 0.098* | 0.754 | NS |
| | Yes | 6 (20.0%) | 7 (23.3%) | | | |
| **Clock (Circle)** | No | 0 (0.0%) | 0 (0.0%) | – | – | – |
| | Yes | 30 (100.0%) | 30 (100.0%) | | | |
| **Clock (Numbers)** | No | 18 (60.0%) | 5 (16.7%) | 11.915* | 0.001 | HS |
| | Yes | 12 (40.0%) | 25 (83.3%) | | | |
| **Clock (Arrows)** | No | 26 (86.7%) | 24 (80.0%) | 0.480* | 0.488 | NS |
| | Yes | 4 (13.3%) | 6 (20.0%) | | | |
| **Naming** | | | | | | |
| **Lion** | No | 0 (0.0%) | 0 (0.0%) | – | – | – |
| | Yes | 30 (100.0%) | 30 (100.0%) | | | |
| **Rhinoceros** | No | 24 (80.0%) | 24 (80.0%) | 0.000* | 1.000 | NS |
| | Yes | 6 (20.0%) | 6 (20.0%) | | | |
| **Camel** | No | 0 (0.0%) | 0 (0.0%) | – | – | – |
| | Yes | 30 (100.0%) | 30 (100.0%) | | | |
| **Attention** | | | | | | |
| **Direct count** | No | 16 (53.3%) | 13 (43.3%) | 0.601* | 0.438 | NS |
| | Yes | 14 (46.7%) | 17 (56.7%) | | | |
| **Reverse count** | No | 20 (66.7%) | 18 (60.0%) | 0.287* | 0.592 | NS |
| | Yes | 10 (33.3%) | 12 (40.0%) | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Reaction (clap to the letter A)** | No | 6 (20.0 %) | 0 (0.0% ) | 6.667 * | 0.010 | S |
| | Yes | 24 (80.0 %) | 30 (100.0 %) | | | |

P-value > 0.05: Non-significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant
*: Chi-square test

**Table 2:** Comparison between two groups in MoCA test results.

| | | Group I No. = 30 | Group II No. = 30 | Test value | P-value | Sig. |
|---|---|---|---|---|---|---|
| **Concentration (Serial account)** | 1 | 8 (26.7 %) | 6 (20.0 %) | 4.571* | 0.102 | NS |
| | 2 | 12 (40.0 %) | 6 (20.0 %) | | | |
| | 3 | 10 (33.3 %) | 18 (60.0 %) | | | |
| **Language** | | | | | | |
| **Repeating sentence 1** | No | 26 (86.7 %) | 24 (80.0 %) | 0.480* | 0.488 | NS |
| | Yes | 4 (13.3 %) | 6 (20.0 %) | | | |
| **Repeating sentence 2** | No | 22 (73.3 %) | 12 (40.0 %) | 6.787* | 0.009 | HS |
| | Yes | 8 (26.7 %) | 18 (60.0 %) | | | |
| **Fluency of speech** | No | 30 (100.0%) | 27 (90.0 %) | 3.158* | 0.076 | NS |
| | Yes | 0 (0.0 %) | 3 (10.0 %) | | | |
| **Abstract thinking** | 0 | 8 (26.7 %) | 0 (0.0 %) | 14.087* | 0.001 | HS |
| | 1 | 22 (73.3 %) | 24 (80.0 %) | | | |
| | 2 | 0 (0.0 %) | 6 (20.0 %) | | | |
| **Memory (Delayed playback)** | Median (IQR) | 1 (1 – 2) | 3 (1 – 3) | -1.643≠ | 0.100 | NS |
| | Range | 0 – 4 | 0 – 4 | | | |
| **Orientation** | Median (IQR) | 5 (4 – 6) | 6 (5 – 6) | -2.890≠ | 0.004 | HS |
| | Range | 3 – 6 | 5 – 6 | | | |
| **MoCA test score** | Mean ± SD | 15.53 ± 2.90 | 19.13 ± 3.41 | -4.406• | 0.000 | HS |
| | Range | 11 – 20 | 13 – 23 | | | |

P-value > 0.05: Non-significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant
*: Chi-square test; F: Fisher's Exact test; •: Independent t-test; ≠: Mann-Whitney test

**Table 3:** Comparison between the two groups in the rest of MoCA test results.

(Table 1) shows sociodemographic factors as well as the length of substance usage. Regarding mean age, education level, marriage, and occupation, no statistically significant differences were detected between the groups (Table 1). Regarding drug use duration, there was a significant difference between the SC group (Group 1) and the cannabis group (Group 2) (Table 1).
Regarding MoCA test total scores, the SC group scored significantly lower than the cannabis group with mean score of 15.53 ± 2.90SD among SC group and of 19.13 ± 3.41SD among cannabis group.

Regarding visuospatial and constructive abilities, there was statically significant difference between the two groups in drawing a clock (numbers) test with lower scores in SC group, and there was non-statically significant difference between the two groups in drawing a broken line, copying a cube test and drawing a clock (circle and arrows) (Table 2).

Regarding naming scores, there was no difference in Rhinoceros, Lion or Camel naming.

Regarding attention and concentration there was significant difference between the two groups in vigilance (reaction clap to letter A) and non-significant difference in direct count, reverse count (Table 2) and serial account (Table 3).
There was significant difference between two groups in repeating sentence 2, abstract thinking and orientation with lower scores in SC group (group 1) and non-significant difference in repeating sentence 1 and fluency of speech between the two groups (Table 3)

Also, regarding delayed playback (delayed recall) testing short-term memory affection, both groups affected with median score of 1 out of 5 among SC group, IQR was 1-2 and among cannabis group median score was 3 out of 5 and IQR was 1-3, although there was a difference between the two groups in scores with lower scores in SC group, the difference was non-statically significant (Table 3)

## DISCUSSION

This presented Study tested Visuospatial and constructive abilities by cube drawing test, drawing a broken line and clock drawing test and they revealed affected abilities in both groups and non-statically significant difference between the two groups in cube drawing test and drawing a broken line test and highly Statically Significant difference between two groups mainly in drawing a clock test (visuospatial ability), which is higher in group 2 using cannabis and this went in agreement with one study [3] which also revealed affection of visuospatial ability caused by cannabinoids use more than healthy control group. Also, there have been several research that link cannabis consumption to cognitive impairment. Significant impairments in visual spatial perception, spatial recognition memory, visual information processing speed, and visual working memory were found in chronic cannabis users in one of these studies when compared to the healthy group, which is Compatible with our results regarding visuospatial ability [5, 3]

In our study, we used direct count and Reaction clap to letter A to test attention, serial account to test sustained attention (concentration), results revealed statically significant difference in attention (using reaction clap to letter A) between the two groups, and there was non-statically significant difference between the two groups in direct count and serial account. More affected attention in the first group (using synthetic cannabinoids with or without cannabis) went in agreement with one study [3] which revealed decreased attention in the group using synthetic cannabinoids. Our findings were in line with those of prior studies looking into the effects of SC. Disruption of fine motor skills, deterioration of attention, and concentration were documented in a case series of seven people driving under the effect of SC [6]. In two preclinical experiments with rats, acute taking of SC agonists WIN55212-2 resulted in reduced performance on a reaction time challenge [7,3] and in two-choice response time tasks, the CB1 agonist AM4054 hindered sustained attention [8] The role of CB1 receptors, which have a dense distribution in the anterior cingulate and cerebellum, could explain why SC users do poorly in attention activities [9].

The volume of the grey matter was found to be decreased in both right and left thalami, as well as the left cerebellum, in brain imaging studies in SC abusers [10], while white matter volume was found to be reduced in the anterior thalamic radiation [11]. The thalamus and anterior cingulate cortex play essential roles in attention processes [12]. In the light of these findings, deficiencies in all attention functions tested in SC users are supported by defects in several brain regions indirectly found in SC abusers in brain imaging investigations. [13]

In our study, there was no difference in the ability to maintain attention (concentration), which contrasts with one study [3], in which the SC group had a significantly greater number of total errors than the cannabis group. This can be explained by the fact that we used a different test, different onset of cannabis use between two studies and differences in synthetic cannabinoid components in between two countries [7, 3].

As regards memory function, we used reverse count to test working memory and delayed playback to test short-term memory in our study, and the results showed that both groups had impaired memory. This is consistent with other studies that have found impairment associated with acute [14] and chronic cannabis use[7]. Acute cannabis use decreased knowledge recall and recognition function, according to one of the most recent reviews [1]. Our findings contradicted two studies [2,3], which found non-statistically significant differences between two groups in working memory and short-term memory. This could be explained by the different tests used, the fact that they tested female and male patients in one study, whereas we only tested males, and the fact that they did not exclude patients with alcohol consumption habits or abuse in one study, which we did, different synthetic cannabinoid components between different countries, and different duration, amount and age of onset of cannabis and synthetic cannabinoid abuse, all of which could be factors explaining the differences.

In addition, our research found a highly significant difference between the two groups in language (repeating sentence 1), orientation, and abstraction abilities, which aligned with 2 studies that found impairment in executive functions in both cannabis and synthetic cannabinoids groups, with synthetic cannabinoids showing more affection for executive functions [2,3].

This study found a highly significant difference in total MoCA test score between the two groups, indicating more cognitive dysfunction in the synthetic cannabinoid group (with or without cannabis). This was consistent with the previous two studies, both of which found more cognitive dysfunction in the synthetic cannabinoid group. [2,3]

There could be a variety of reasons for the higher effects of SC on cognition when compared to THC. Although SCs bind to the same endogenous cannabinoid receptors (CB1 and CB2) as cannabis, recent research has shown that they also bind to TRPV1 receptors [16] or affect non-cannabinoid receptors by forming heterodimers between CB1 and D2 dopamine, -opioid, or orexin-1 receptors [17,18]. SCs may produce more severe deficits in cognitive functioning than cannabis because they impact many receptors other than those activated by cannabis. It was discovered that cannabidiol, a component of marijuana, has neuroprotective properties [19]. Based on this evidence, the truth that SC abusers are missing out on cannabidiol's neuroprotective properties could explain why they have more potential cognitive deficits. Other psychoactive chemicals in SC-containing products may also cause cognitive deficits due to the varied structure of these items. Another explanation could be because people with SC use disorder use substances more frequently, resulting in more intense withdrawal symptoms. A higher frequency of use may have a greater impact on cognitive processes [3].

There are some limitations to this study. Firstly, Due to the increased cost of urine toxicological screening and the lack of funding for the trial, the number of patients in each group was reduced. Secondly, all the patients in the study were male (female abusers may have a different cognitive profile), so these findings cannot be generalized to all SC abusers. Thirdly, our study included patients who used synthetic cannabinoids with or without cannabis, and patients who used cannabis before synthetic cannabinoids, which may have influenced the results. Fourthly, there are various types of SCs, and there is a lack of information on the influence of different types, as well as which types the patients abused. Also, although we performed a comprehensive psychiatric assessment and excluded psychiatric disorders, we did not use any scale to evaluate psychiatric disorders. Another limitation of our study could be the length of abstinence before administering the MoCA test.

## CONCLUSION

Impairments in cognitive functions as attention, language, orientation, abstract thinking, executive and visual-spatial functions were found in SC abusers (with or without cannabis) as a result of our research, and these impairments were found to be significantly higher than in others abusing cannabis only. Significance of the present study emerged from the point that it gives a broad picture of changes in cognitive processes among SC users; nevertheless, more complete batteries must be used to test each cognitive function, and these investigations must be accompanied by sensitive brain imaging studies. Future research should look into the relation between the amount, length, and frequency of SC abuse and cognitive function decline, as well as whether cognition get better after long-term abstinence. More studies are needed to investigate the link between the amount, duration, and frequency of SC usage and cognition, as well as longitudinal studies to look into long-term consequences.

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