



ORIGINAL ARTICLE

Cannabinoid Use and Depression: Comparison of Natural and Synthetic Cannabinoids

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Abstract

Purpose: Patients who predominantly used marijuana (natural cannabis) and patients who predominantly used synthetic cannabinoids in their history were evaluated as two separate groups in our study which aimed to compare the sociodemographic characteristics and depressive symptoms of these two groups.

Method: The sample of our study consisted of those patients who referred to the Polyclinic of Psychiatry at Ardahan State Hospital and were diagnosed with substance addiction. 30 polyclinic patients who defined predominant use of marijuana and 20 polyclinic patients who defined predominant use of synthetic cannabinoids (bonzai, Jamaika, etc.) (SC) were included in the study. The socio-demographic characteristics of the participants were determined, and the depressive symptoms were assessed by the Beck Depression Inventory.

Results: Our study determined the socio-demographic characteristics of the marijuana-using group and the synthetic-cannabinoid-using group as similar. The depression score of the group using synthetic cannabinoids was found to be significantly higher.

Discussion: In our study, findings pointing to the fact that cannabinoid use increases depressive symptoms and that synthetic cannabinoids have a strong depressive side effect have been obtained. The cross-sectional characteristic of the study and the low number of subjects constitute the limitations.

Keywords

Marijuana, Synthetic cannabinoids, Depression

drocannabinol (THC) [1]. Synthetic cannabinoids (SC) constitute a sub-group of cannabinoids and are among those psychoactive substances that enjoy an increased popularity of use. Narcotic drugs involving synthetic cannabinoids are known as “Bonzai” or “Jamaika” in Turkey [1].

Two types of cannabinoid receptors called Cannabinoid 1 (CB1) and Cannabinoid 2 (CB2) have been determined in the human body. The CB1 receptors mainly exist in the neurons of the brain, spinal cord and peripheral nervous system, whereas the CB2 receptors mostly exist in immune cells such as leukocytes, the spleen and tonsils. Cannabinoids have varying degrees of affinity to CB1 and CB2 receptors. THC has approximately equal affinity to CB1 and CB2 receptors whereas synthetic cannabinoids are produced as agonists or antagonists having selectivity towards one of these receptors [2].

The activation of the cannabinoid system results in various effects such as elevated mood, anxiety, depersonalization, hallucinations, changed time perception and memory failure [2]. *In vitro* studies and studies conducted on animals have shown that synthetic cannabinoids have similar pharmacological features with THC, however synthetic cannabinoids have higher affinity to cannabinoid receptors and specifically to SC 1. [3,4] THC has a partial agonistic effect as well as a plateau effect, since an increase in the amount of substance used does not create any difference on the effect. Synthetic cannabinoids are full agonists that bind to receptors with high potency and affinity. Lack of plateau effect in synthetic cannabinoids results in an

Introduction

Marijuana (natural cannabis) is the most commonly used illicit drug according to many studies. The main psychoactive component of marijuana is $\Delta 9$ -tetrahy-

increase in the effects caused by the substance. Synthetic cannabinoids have similar psychoactive effects with THC, however their effects are stronger compared to natural cannabinoids [5].

Substances involving synthetic cannabinoids also involve preservatives, fatty acids, amides, esters, benzodiazepines and O-desmethyltramadol which is the main active metabolite of tramadol. The additional components are usually added to increase the psychoactive effect of the substance and mask the main psychoactive content in testing [6].

In psychiatric patients, the comparison of natural cannabis users with synthetic cannabinoid users has revealed that the synthetic-cannabinoid-using group demonstrates more severe psychotic symptoms and agitation [7,8]. It is known that long-term natural cannabinoid use increases the risk of development of mental disorders such as anxiety, depression, bipolar disorder and schizophrenia [9-11]. On the other hand, evidences about the negative psychiatric and medical results of synthetic cannabinoid use have been increasing. It has also been reported that the negative side effects of repetitive use of synthetic cannabinoids are more severe and long-lasting than those of natural cannabinoids [11]. It has been determined that synthetic cannabinoid users experience more anxiety, paranoia and depressive symptoms than natural cannabinoid users [12]. In a study that compared synthetic cannabinoid users and natural cannabinoid users, it was determined that synthetic cannabinoid users reported psychopathological symptoms 3.5 to 5 times more [13].

Effects of marijuana and synthetic cannabinoids have been studied and the issue is of great interest however it is very difficult to determine the actual frequency of use, properties of use and their effects on society and the individual. Also, there is a lack in the literature about the comparison of depression, which leads to a serious decrease in quality of life, in natural and synthetic cannabinoid users. In our study, it was planned to include patients who referred to a psychiatry polyclinic and reported predominant use of marijuana or synthetic cannabinoids (bonzai, Jamaika, etc.). It was aimed to determine the sociodemographic characteristics, living conditions and motivation for starting substance use in individuals meeting the criteria for Substance Use Disorder diagnosis. It was predicted that depressive symptoms in such individuals would be high. Again, in consideration of the effect mechanisms of synthetic cannabinoids and marijuana, it was considered that depressive symptoms would be more severe in the group predominantly using synthetic cannabinoids.

Material and Method

Our study was conducted in Turkey among male pa-

tients who referred to the Polyclinic of Psychiatry at Ardahan State Hospital during a 1-year period (July 2013 - July 2014). Those patients who specified marijuana or synthetic cannabinoid (bonzai, Jamaika, etc.) use and met the Substance Use Disorder criteria according to DSM 5 were included in the study.

Our study received the approval of the local ethics committee. The patients were informed about the study, and those who accepted to take part in the study were examined by clinicians. All procedures contributing to this work complied with the ethical standards of the relevant national and institutional committees on human experimentation as well as the Helsinki Declaration of 1975, as revised in 2008.

The socio-demographic data of the participants such as age, education, marital status, employment - income status and place of living were obtained. Further, the participants were also questioned with regard to social support, ability to lead their lives alone, age and reason for onset of substance use, the longest pause to substance use, any past legal problems experienced and any behavior of self-harm.

The depression levels of all participants were determined by the Beck Depression Inventory which consists of 21 items measuring the emotional, somatic, cognitive and motivational symptoms of depression. The version created by Beck in 1978 was adapted into Turkish by Hisli [14,15].

The data obtained was subjected to statistical analysis by using the SPSS Statistics 15.0 program. The demographic data was examined by Chi-square and Fisher's Exact test. The scale scores were evaluated by Mann Whitney U test. In all these analyses, the statistical significance level was taken as $p < 0.05$.

Results

Our study included 30 (60%) male patients who predominantly defined marijuana use and 20 (40%) male patients who predominantly defined synthetic cannabinoid (bonzai, Jamaika, etc.) (SC) use. Both marijuana-using group and SC-using group declared that the frequency of substance use was at least 3 times a week. The median value for age in the SC-using group was determined as 20 whereas it was determined as 22 in the marijuana-using group. A significant difference was determined between the two groups in terms of age ($p = 0.004$) (Table 1).

Among the SC users, 10% ($n = 2$) were married, 85% ($n = 17$) were single and 5% were divorced or widowed ($n = 1$), whereas among the marijuana users, 13.3% ($n = 4$) were married and 86.7% ($n = 26$) were single. As for educational status, in the SC-using group, 70% ($n = 14$) had primary education and 30% had high school degree ($n = 6$) whereas in the marijuana-using group, 66.7% ($n = 20$) had primary

Table 1: Age distribution.

| | Synthetic Cannabinoid | | | | Marijuana | | | | Z | p |
|-------------------------|-----------------------|--------|-------|-------|-----------|--------|-------|-------|--------|-------|
| | N | Median | Min | Max | N | Median | Min | Max | | |
| Age | 20 | 20.00 | 19.00 | 23.00 | 30 | 22.00 | 19.00 | 28.00 | -2.902 | 0.004 |
| Drug Starting Age | 20 | 15.00 | 12.00 | 17.00 | 30 | 15.50 | 10.00 | 20.00 | -1.049 | 0.294 |
| First Legal Problem Age | 14 | 16.00 | 14.00 | 19.00 | 22 | 16.00 | 12.00 | 18.00 | -0.937 | 0.349 |

Table 2: Socio-Demographic features.

| | Synthetic Cannabinoid | Marijuana | Total | |
|-----------------------------------|-----------------------|------------|----------|---------|
| Educational status | | | | p 0.804 |
| Primary Education | 14 (70%) | 20 (66.7%) | 34 (68%) | |
| High School Degree | 6 (30%) | 10 (33.3%) | 16 (32%) | |
| Marital Status | | | | n/a |
| Married | 2 (10%) | 4 (13.3%) | 6 (12%) | |
| Single | 17 (85%) | 26 (86.7%) | 43 (86%) | |
| Divorced or widowed | 1 (5%) | - | 1 (2%) | |
| Working Status | | | | p 0.279 |
| Employed | 2 (10%) | 8 (26.7%) | 10 (20%) | |
| Not Employed | 18 (90%) | 22 (73.3%) | 40 (80%) | |
| Income Rate | | | | p 0.069 |
| Under 1000 TL | 20 (100%) | 24 (80%) | 44 (88%) | |
| Between 1000-2000 TL | - | 6 (20%) | 6 (12%) | |
| Ability to lead their lives alone | | | | p 0.355 |
| Can live alone | 8 (40%) | 16 (53.3%) | 24 (48%) | |
| Can't live alone | 12 (60%) | 14 (46.7%) | 26 (52%) | |
| Felt Social Support | | | | p 0.797 |
| Exist | 6 (30%) | 8 (26.7%) | 14 (28%) | |
| Not Exist | 14 (70%) | 22 (73.3%) | 36 (72%) | |
| Legal Problem | | | | p 0.797 |
| Exist | 14 (70%) | 22 (73.3%) | 36 (72%) | |
| Not Exist | 6 (30%) | 8 (26.7%) | 14 (28%) | |
| Self Mutilation | | | | p 1.000 |
| Exist | 18 (90%) | 26 (86.7%) | 44 (88%) | |
| Not Exist | 2 (10%) | 4 (13.3%) | 6 (12%) | |

education and 33.3% (n = 10) had high school degree, thus no difference was observed between the two groups in this regard. It was observed that the majority of the participants lived with their families (the SC group 100%, the marijuana group 80%). In the SC-using group 90% (n = 18) and in the marijuana-using group 73.3% (n = 22) indicated that they were not employed. The entirety of the SC-using group (n = 20) and 80% (n = 24) of the marijuana-using group stated their monthly income as TRY 1000 or less (Table 2).

Among the participants, 48% indicated that they could live alone if they chose to whereas 52% stated that they would not be able to go on with their lives alone. No significant differences were observed between the SC-using group and the marijuana-using group in terms of the ability to lead their lives alone. (p = 0.355) The felt social support was similar in the two

groups (p = 0.797) as 28% expressed the existence of social support. Among the cases, 88% (n = 44) previously committed self-harm whereas 72% (n = 36) reported experiencing legal problems at least once in their lifetime. No significant difference was determined between the two groups in terms of defined risky behavior (Table 2). When the participants who got involved in crime were questioned in terms of the age of first legal problem, it was determined that the SC group was first involved in crime at the minimum age of 14 and maximum age of 19 (median 16) and the marijuana group at the minimum age of 12 and maximum age of 18 (median 16). No significant difference was determined between the two groups in terms of the age of first legal problem experienced (p = 0.349) (Table 1).

As for the reason for starting substance use, 4% (n = 2) mentioned curiosity, 72% (n = 36) alleviation of dis-

Table 3: Substance use characteristics.

| | Synthetic Cannabinoid | Marijuana | Total | |
|-----------------------------------|-----------------------|------------|----------|-----|
| Reason for Starting Substance use | | | | |
| Curiosity | - | 2 (6.7%) | 2 (4%) | n/a |
| Alleviation of distress | 18 (90%) | 18 (60%) | 36 (72%) | |
| Suggestion/insistence of friends | 2 (10%) | 6 (20%) | 8 (16%) | |
| Other | - | 4 (13.3) | 4 (8%) | |
| Longest Time Without Substance | | | | |
| Never discontinued use | 8 (40%) | 10 (33.3%) | 18 (36%) | n/a |
| Between 1 week - 1 month | 10 (50%) | 6 (20%) | 16 (32%) | |
| Between 1 month - 6 months | 2 (10%) | 12 (40%) | 14 (28%) | |
| More than 6 months | - | 2 (6.7%) | 2 (4%) | |

Table 4: Beck depression scale scores.

| | Synthetic Cannabinoid | | | | Marijuana | | | | Z | p |
|---------------------------|-----------------------|--------|-------|-------|-----------|--------|-------|-------|--------|-------|
| | N | Median | Min | Max | N | Median | Min | Max | | |
| Beck Depression Inventory | 20 | 41.00 | 30.00 | 56.00 | 30 | 36.00 | 22.00 | 50.00 | -2.212 | 0.027 |

trass, 16% (n = 8) suggestion/insistence of friends, and 8% (n = 4) other reasons. Among the users of synthetic substances, 40% (n = 8) indicated that they never discontinued use whereas 50% (n = 10) indicated a pause for a maximum of 1 week - 1 month, and 10% (n = 2) for a maximum of 1-6 month(s), 33% (n = 10) of the marijuana-using group indicated that they never discontinued substance use whereas 32% (n = 16) reported a pause for a maximum of 1 week - 1 month, 28% (n = 14) for a maximum of 1-6 month(s) and 4% (n = 2) for more than 6 months (Table 3). The age of onset of substance use was determined as minimum 12 and maximum 17 (median = 15) in the SC-using group, and minimum 10 and maximum 20 (median = 15.50) in the marijuana-using group (Table 1).

In the Beck Depression Inventory performed, the scores of the cases varied between 30-56 points (median = 41) in the SC-using group, and between 22-50 (median = 36) in the marijuana-using group. It was observed that the Beck Depression scores of the SC-using group were higher, leading to the detection of a significant difference compared to the marijuana-using group (p = 0.027) (Table 4).

Discussion

Our study was performed among a clinical sample using substance at least 3 times a week and seeking aid against substance use.

In our study, the participants consisted solely of men. It is considered that this distribution has been affected by sociocultural influences and the fact that our study was a cross-sectional one based on polyclinic application.

Among the patients who participated in the study, the group using synthetic cannabinoids was determined to have lower median age. It has been as-

sessed that the greater negative effects of synthetic cannabinoid use compared to marijuana use might have affected the behavior of seeking treatment and caused early application. On the other hand, it should be taken into consideration that the cross-sectional analysis of the patients who referred to the polyclinic in our study might have affected our results.

It was observed that the majority of the participants were primary school graduates. The educational level in our sample was similar to those of previous studies in Turkey [16-18]. No significant difference was observed between the educational levels of the two groups in our study.

It was observed that the employment rates were low, and the patients subsisted on a monthly income of TRY 1000 or less in both the synthetic-cannabinoid-using and the marijuana-using groups. It is evaluated that irrespective of the substance used, substance use in general negatively affects patients' participation in social life and production [16,19].

No difference was observed between the marijuana-using group and the synthetic-cannabinoid-using group in terms of the felt social support. The fact that the demographic characteristics and social support were similar in the two groups increased the comparative power of our study.

In the neuroimaging studies conducted, it was observed that cannabis use led to a mild but significant increase in the striatal dopamine levels. An increase in the striatal dopamine release was detected in the group having cannabis addiction. Synthetic cannabinoids may be anticipated to entail an increased addiction risk as they have a more potent effect on the endocannabinoid system compared to marijuana [13,20,21]. In our study, although there was no spe-

cific method to measure addiction risk, the fact that most of the cases started substance use younger than 18 years of age and only 2 participants in the marijuana-using group discontinued substance use for a period longer than 6 months provides an idea about the addiction potential. In both groups, most of the participants were only able to discontinue substance use for a period shorter than 6 months.

The most frequently uttered reason for cannabinoid use is “curiosity” [22], yet in our study, “alleviating distress” came first. It is considered that the fact that our sample involved those patients who voluntarily sought treatment was effective. In a similar study conducted on patients who voluntarily applied for treatment, the most frequently uttered reason for cannabinoid use had been determined to be “the sense of relaxation it creates” [22].

It was observed that the majority of the participants had been involved in crime at least once in their lifetime and engaged in self-harm. The pre-morbid characteristics most commonly associated with substance use disorder comprise borderline and anti-social personalities in which impulsivity stands out. Such personality traits will cause problems in obeying legal and social rules also before the onset of substance use. Additionally, the correlation between substance use and committing crimes has been analyzed in various studies. Although more limited, the studies conducted in Turkey have revealed such correlation [16,23]. Our cases included patients who got involved in crime after the onset of substance use as well as those who committed their first crimes before starting substance use. No differences were observed between the two groups in terms of crime involvement and self-harm behavior.

It has been argued that the partial agonistic effect of Δ 9-tetrahydrocannabinol (THC), the ingredient in marijuana, on Cannabinoid 1 (CB1) and Cannabinoid 2 (CB2) is responsible for the psychoactive effects. On the other hand, synthetic cannabinoids are generally more potent cannabinoid receptor agonists compared to THC [11]. There is a well-known correlation between cannabis use and psychosis [24]. Considering the potent psychoactive effects of synthetic cannabinoids, it would not be surprising to observe cases of psychosis caused by acute or constant use of synthetic cannabinoid-involving substances [11,25]. Psychotic conditions, schizophrenia and mood disorders are the prominent psychiatric side effects of cannabinoids [3,11,24]. It is considered that users of synthetic cannabinoids would experience almost all side effects more severely owing to the effect mechanisms. In a self-report study comparing patients using synthetic cannabinoids with those using natural cannabis, somatization, obsessive-compulsive symptoms, depression, anxiety, phobias, paranoid thoughts and

psychoticism were analyzed, and all psychiatric symptoms were determined to be higher in synthetic cannabinoid users [13].

In view of the identified effect mechanisms and high psychoactive effects of synthetic cannabinoids, these findings correspond to the previous literature data. On the other hand, depressive symptoms have had more limited place in the literature. The strength of our study lies in the fact that it was conducted in a clinical sample seeking aid against substance use and handled depression in different groups of cannabinoid users. The limitation of our study is the fact that it was conducted cross-sectionally at a single center. It is considered that multi-centered and prospective studies are needed in this regard.

Conclusions

It was observed that in our sample, the Beck Depression scores were high in all participants. As for the comparison of the two groups, the Beck Depression scores of the group predominantly using synthetic cannabinoids were found to be significantly higher. Given serious side effects, the widespread use of cannabinoids is a growing problem. Depressive symptoms are significant due to their disrupting effects on functionality and quality of life. In clinical practice, dealing with depression should be a part of medical programs when treating cannabinoid use disorder.

Author Contributions

Conceptualization: Serap Akdeniz Görgülü, Can Sait Sevindik; Data curation: Serap Akdeniz Görgülü; Formal analysis: Serap Akdeniz Görgülü, Can Sait Sevindik; Investigation: Can Sait Sevindik; Project administration: Serap Akdeniz Görgülü, Can Sait Sevindik; Writing - Original draft: Serap Akdeniz Görgülü; Writing - review & editing: Serap Akdeniz Görgülü, Can Sait Sevindik.

References

1. Pakiş I, Polat O (2016) Sentetik Kannabinoidler. *ACU Sağlık Bil Derg* 2016: 6-13.
2. Grotenhermen F (2003) Pharmacokinetics and pharmacodynamics of cannabinoids. *Clin Pharmacokinet* 42: 327-360.
3. Castaneto MS, Gorelick DA, Desrosiers NA, Hartman RL, Pirard S, et al. (2014) Synthetic cannabinoids: epidemiology, pharmacodynamics, and clinical implications. *Drug Alcohol Depend* 144: 12-41.
4. Martinotti G, Santacroce R, Papanti D, Elgharably Y, Pri-lutskaya M, et al. (2017) Synthetic cannabinoids: psychopharmacology, clinical aspects, psychotic onset. *CNS Neurol Disord Drug Targets* 16: 567-575.
5. Geller T (2007) Cannabinoids: A secret history. *Chem Herit Newsmagazine*, 25.
6. Fattore L, Fratta W (2011) Beyond THC: The new generation of cannabinoid designer drugs. *Front Behav Neurosci* 5: 60.

7. Bassir Nia A, Medrano B, Perkel C, Galynker I, Hurd YL (2016) Psychiatric comorbidity associated with synthetic cannabinoid use compared to cannabis. *J Psychopharmacol* 30: 1321-1330.
8. Shalit N, Barzilay R, Shoval G, Shlosberg D, Mor N, et al. (2016) Characteristics of synthetic cannabinoid and cannabis users admitted to a psychiatric hospital: A comparative study. *J Clin Psychiatry* 77: e989-e995.
9. Moore THM, Zammit S, Lingford-Hughes A, Barnes TRE, Jones PB, et al. (2007) Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review. *Lancet* 370: 319-328.
10. Volkow ND, Baler RD, Compton WM, Weiss SRB (2014) Adverse health effects of marijuana use. *N Engl J Med* 370: 2219-2227.
11. Cohen K, Weinstein AM (2018) Synthetic and Non-synthetic cannabinoid drugs and their adverse effects-a review from public health perspective. *Front Public Health* 6: 162.
12. Akram H, Mokrysz C, Curran HV (2019) What are the psychological effects of using synthetic cannabinoids? A systematic review. *J Psychopharmacol* 33: 271-283.
13. Mensen VT, Vreeker A, Nordgren J, Atkinson A, de la Torre R, et al. (2019) Psychopathological symptoms associated with synthetic cannabinoid use: A comparison with natural cannabis. *Psychopharmacology (Berl)* 236: 2677-2685.
14. Hisli N (1988) Beck Depresyon Envanteri'nin geçerliği üzerine bir çalışma. *Psikoloji Dergisi* 6: 118-126.
15. Hisli N (1989) Beck Depresyon Envanteri'nin üniversite öğrencileri için geçerliği, güvenilirliği. *Psikoloji Dergisi* 7: 3-13.
16. Asan Ö, Tıkır B, Okay İT, Göka E (2015) Bir AMATEM Birimine Başvuran Alkol ve Madde Kullanım Bozukluğu olan Hastaların Sosyodemografik ve Klinik Özellikleri. *Bağımlılık Dergisi* 16: 1-8.
17. Beyazyürek M, Alpkan L, Karamustafaloğlu KO ve ark (1990) Uyuşturucu madde bağımlılarında sosyodemografik özellikler. *Düşünen Adam* 3: 59-61.
18. Alpay N, Maner F, Kalyoncu A (1991) AMATEM'de 1990 yılında yatırılan madde bağımlılarının demografik özellikleri ve geçmiş yıllarla kıyaslanması. 27. Ulusal Psikiyatri Kongresi Program ve Bildiri Özetleri Kitabı, 177.
19. Öznur T, Öznur H, Bolu A, Çelik C, Özmenler KN (2018) Sociodemographic and clinical features of young adult males using synthetic cannabinoid. *Turkish J Clinical Psychiatry* 21: 15-23.
20. Bossong MG, van Berckel BNM, Boellaard R, Zuurman L, Schuit RC, et al. (2009) Delta 9-tetrahydrocannabinol induces dopamine release in the human striatum. *Neuropsychopharmacology* 34: 759-766.
21. Van de Giessen E, Weinstein JJ, Cassidy CM, Haney M, Dong Z, et al. (2017) Deficits in striatal dopamine release in cannabis dependence. *Mol Psychiatry* 22: 68-75.
22. Bozkurt M, Umut G, Evren C, Karabulut V (2014) Sentetik Kannabinoid Kullanımı Nedeniyle Polikliniğe Başvuran Hastaların Klinik Özellikleri ve Laboratuvar Sonuçları. *Düşünen Adam The Journal of Psychiatry and Neurological Sciences* 27: 328-334.
23. Altuner D, Engin N, Gürer C, Akyay İ, Akgül A (2009) Madde kullanımı ve suç ilişkisi: kesitsel bir araştırma. *Tıp Araştırmaları Dergisi* 7: 87-94.
24. Volkow ND, Swanson JM, Evins AE, DeLisi LE, Meier MH, et al. (2016) Effects of cannabis use on human behavior, including cognition, motivation, and psychosis: a review. *JAMA Psychiatry* 73: 292-297.
25. Davidson C, Opacka-Juffry J, Arevalo-Martin A, Garcia-Ovejero D, Molina-Holgado E, et al. (2017) Spicing up pharmacology: A review of synthetic cannabinoids from structure to adverse events. *Advances in Pharmacology* 80: 135-168.