

## Concomitant substance use increases the toxic effect of synthetic cannabinoid (bonsai): a prospective study

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**Abstract:** *Objective:* In this study, we aimed to contribute to the literature by evaluating synthetic cannabinoid (bonsai) and additional drugs. *Materials and Methods:* This prospective study was conducted on 217 patients who admitted to the emergency department (ED) with bonsai intake between December 20, 2014 and January 1, 2016, according to the patient history obtained from the patients. One hundred sixty-eight patients with negative urinary metabolites results were excluded from the study, 49 patients with positive urinary metabolites were included in the study. Patients were divided into two groups. The first group consisted of patients with only bonsai intake and the second group consisted of patients with bonsai and concomitant drug intake. The groups were compared in terms of symptoms, findings, blood gas values, duration of the symptoms, discharge time, hospitalization, and mortality rate. Data were analyzed using the Chi-square, the Fisher's exact test, the Student t-test, and the Mann-Whitney U test. Data were evaluated at the 95% confidence interval.  $P < 0.05$  was considered statistically significant. *Results:* The mean age of 49 patients included in the study was  $26.7 \pm 8.9$  years and 91.8% ( $n=45$ ) of the patients were male. Concomitant drug intake was identified in 69.4% of the patients. Concomitant drug use was as follows: cocaine (20.4%,  $n=10$ ), amphetamines (14.3%,  $n=7$ ), methamphetamines (8.2%,  $n=4$ ), tetrahydrocannabinol (32.7%,  $n=16$ ), opiates (18.4%,  $n=9$ ) and alcohol (30.6%,  $n=15$ ). On admission, the Glasgow Coma Score (GCS) in the bonsai group with an additional substance was significantly higher ( $p=0,003$ ). The most common symptom was palpitations (tachycardia) (75.5%,  $n=37$ ). There were no patients hospitalized in the Only Bonsai group ( $p=0,020$ ). The median time to remission of symptoms and median follow-up time of the patients in the emergency room were 3 hours and 6 hours, respectively. Remission time of the symptoms and hospitalization rates were higher in patients taking concomitant drug ( $p < 0.05$ ). *Conclusion:* While the bonsai intake alone is not considered mortal to the patients and most of them can be discharged from the ED after signs and symptoms disappear, concomitant drug use can increase the toxic effects of bonsai intake. That is why the follow-up of patients taking concomitant drugs, and the treatment process should be carried out more carefully. ([www.actabiomedica.it](http://www.actabiomedica.it))

**Keywords:** Substance abuse, Bonsai, Toxic effect

## Introduction

Synthetic cannabinoids (SC) are chemical substances that cause marijuana-like effects and their intake has increased worldwide in recent years (1,2). “Bonsai”, produced in Europe for the first time in 2004, was touted to society as “harmless”, “legal marijuana” and “designed drug”, and therefore seems to be easily placed on the market (3). In recent years, due to its cannabis effects, availability and low cost, its use has rapidly increased, especially among adolescents and young adults (4, 5). Despite the lack of current data regarding the prevalence of SC use in Turkey, some studies show that the use of SCs is rapidly becoming widespread among the young population in Turkey (4).

The appearance of ‘herbal highs’ in the market is not a new phenomenon. Such products usually consisted of plant mixtures with little psychoactive effects. Since 2004, however, the composition of these herbal products seems to have substantially changed to include potent new psychoactive compounds known as synthetic cannabinoids (bonsai). Since 2004, 11 subgroups of SC produced by different manufacturers were identified (6). The most commonly found SC subgroups on the market are JWH-018, JWH-073, HU-210, and CP-47,497. JWH-018, arguably the most widely known synthetic cannabinoid, belongs to the group of aminoalkylindoles and is considered to be three times as potent as THC (7, 8). Synthetic cannabinoids that have emerged more recently show an even greater structural diversity, e.g APINACA (AKB-48), an adamantyl indazole carboxamide, and AB-PINACA, an aminocarbonyl indazole carboxamide. (9) Depending on different combinations and ratios of these produced SCs, it can be said that predicting clinical effects is very difficult (6). SCs have sympathomimetic effects such as palpitations, sweating, agitation, and restlessness (1). Although pathologies such as acute coronary syndrome (ACS), pulmonary embolism (PE), ischemic stroke, seizures and acute kidney injury (AKI) due to SCs have been reported, there was no evidence whether these findings were caused by SCs or other drugs taken along side with SCs (10-14).

Drug addicts are reported to tend to use multiple substances simultaneously. Due to the fact that this substance has recently been used as a drug, information

about its toxic effects and interactions with other used drugs is quite inadequate (15).

In our study, it was aimed to investigate the epidemiological and clinical characteristics of patients admitted to our ED with “bonsai” intake. In addition, we aimed to investigate the relationship between the use of additional drugs and clinical findings, hospitalization, and mortality.

## Materials and Methods

This prospective study was conducted on 217 patients who admitted to the emergency department between December 20, 2014 and January 1, 2016, due to uncomfortable symptoms that developed after “bonsai” intake.

Urine samples of the patients were analyzed for JWH-18 and JWH-73 metabolites using Rapid K2 Test Card (An immunochromatographic assay for the rapid visual detection of synthetic cannabis (K2) in human urine). One hundred sixty-eight patients with negative urinary metabolites were excluded from the study. Urine samples of the patients with positive urinary metabolites were screened simultaneously for other drugs (acetaminophen, amphetamines, methamphetamines, barbiturates, benzodiazepines, cocaine, methadone, opiates, phencyclidine, tricyclic antidepressants, and tetrahydrocannabinol) using toxicology panel (Alere Triage TOX Drug Screen). Ethanol levels were measured in blood samples taken from the patients.

The demographic characteristics, concomitant drug use, symptoms, findings, arterial blood gas values (pH, pO<sub>2</sub>, pCO<sub>2</sub>, lactate, and base deficit), duration of symptoms, time to discharge, and hospitalization rates of the patients were evaluated. The patients were divided into two groups as follows: namely patients with only “bonsai” intake (Group 1) and patients with “bonsai” and concomitant drug or alcohol intake (Group 2). The groups were compared in terms of symptoms, findings, arterial blood gas values, duration of symptoms, time to discharge, and hospitalization rates.

Data analysis was performed with SPSS 26 for Windows software package. Distributions of continuous and discrete numerical variables were analyzed with the Kolmogorov-Smirnov test. Descriptive statistics for continuous and discrete numeric variables

and categorical variables were expressed as mean  $\pm$  standard deviation, median (min-max). Categorical variables were analyzed using the Chi-square and the Fisher's exact test. The Student t- test and the Mann-Whitney U test were used for analyzing parametric and nonparametric data. Data were evaluated at the 95% confidence interval.  $P < 0.05$  was considered statistically significant.

This study was approved by the Ethical committee of the Antalya Training and Research hospital, and the consent forms were taken from the patients.

## Results

The mean age of 49 patients included in the study was  $26.7 \pm 8.9$  years and 91.8% (n=45) of the patients were male. Patients were determined to be frequently (46.9%, n=23) graduated from primary school. The general aim for using bonsai was for pleasure (69.4%, n=34) and the most common way to use SC was to smoke the mixed bonsai with dried plant material

(81.6%, n=40). Friends were the most common (75.5%, n=37) source of supply and (40.8%, n=20) had experience using bonsai. Additional drug intake was identified in 77.5% (n=38) of the patients. In history, other drug use was as follows: cocaine (59.2%, n=29), heroin (6.1%, n=3) and ecstasy (12.2%, n=6) (Table 1).

Concomitant drug use was as follows: cocaine (20.4%, n=10), amphetamines (14.3%, n=7), methamphetamines (8.2%, n=4), tetrahydrocannabinol (32.7%, n=16), opiates (18.4%, n=9) and alcohol (30.6%, n=15). The most common symptoms in patients in Group 1 were vertigo (56.25%) and confusion (50%), while the most common symptoms in Group 2 were confusion (60.6%) and agitation (48.5%). The most common physical examination findings in Group 1 were tachycardia (87.5%) and redness in eyes (68.8%), while in Group 2, the most common physical examination finding was tachycardia (69.7%). There was no difference in terms of symptoms and signs between two groups except for vertigo; vertigo was more frequent in Only Bonsai Group ( $p=0,038$ ). The most common ECG finding in both groups was Sinus tachycardia (71.4%). While all

**Table 1.** Demographic data

N (%)		N (%)	
<b>Gender</b>		<b>Reason for use</b>	
Female	4 (%8,2)	Pleasure	34 (%69,4)
Male	45 (%91,8)	Increase in sexual desire	7 (%14,3)
<b>Education</b>		Suicidal thoughts	2 (%4,1)
Primary school	23 (%46,9)	Cheap, easy to find	7 (%14,3)
Secondary school	18 (%36,7))	Other	2 (%4,1)
High school	6 (%12,2)	<b>Previous "bonsai" intake</b>	
University	2 (%4,1)	Present	20 (%40,8)
<b>Monthly income</b>		None	29 (%59,2)
Less than 300 USD	41 (%83,7)	<b>Usage type</b>	
More than 300 USD	8 (%16,3)	Cigarette	40 (%81,6)
<b>Psychiatric drug use</b>		Hookah	6 (%12,2)
Present	5 (%10,2)	Incense	1 (%2)
None	44 (%89,8)	Bong	2 (%4,1)
<b>Source of supply</b>		<b>Additional substance</b>	
Internet	3 (%6,1)	Cocaine	29 (%59,2)
Friend	37 (%75,5)	Heroin	3 (%6,1)

patients from Group 1 were discharged from the ED after the examination and treatment, in Group 2, 69.7% of the patients were discharged from the ED and 30.3% were hospitalized. (Patients whose symptoms did not regress or clinically worsen during follow-up in the emergency room and patients whose vital signs were unstable were hospitalized.). It was noteworthy that there were no patients from Group 1 among the hospitalized patients ( $p=0,020$ ). Although exitus was not seen in Group 1 and the mortality rate was found to be 9.1%

in Group 2, there was no statistical difference between the groups in terms of mortality rates. (Table 2).

In all patient groups, blood gas results revealed a normal range of pH, slightly higher PCO<sub>2</sub>, and low PO<sub>2</sub>. When we compare the only bonsai group and the “bonsai” group with additional substance, pH, pO<sub>2</sub>, and glucose levels were lower but pCO<sub>2</sub> and base deficit levels were higher in the bonsai group with additional substance. On admission, the Glasgow coma scale (GCS) in the “bonsai” group with additional

**Table 2.** Comparison of patients' symptoms, findings, death and hospitalization rates

	Group 1		Group 2	P*
	Total	(n=16)	(n=33)	
<b>Concomitant drug use</b>				
Cocaine	10 (%20,4)	-	10 (%30,3)	
Amphetamines	7 (%14,3)	-	7 (%21,2)	
Methamphetamines	4 (%8,2)	-	4 (%12,1)	
Tetrahydrocannabinol	16 (%32,7)	-	16 (%48,5)	
Opiates	9 (%18,4)	-	9 (%27,3)	
Ethanol	15 (%30,6)	-	15 (%45,5)	
<b>Symptoms</b>				
Agitation	21 (%42,9)	5 (%31,3)	16 (%48,5)	0,253
Confusion	28 (%57,1)	8 (%50)	20 (%60,6)	0,482
Coma	9 (%18,4)	1 (%6,3)	8 (%24,2)	0,238
Hallucinations	17 (%37)	7 (%43,8)	10 (%33,3)	0,486
Nausea	21 (%45,7)	7 (%43,8)	14 (%46,7)	0,850
vomiting	16 (%33,3)	5 (%31,3)	11 (%34,4)	0,829
Vertigo	22 (%47,8)	11 (%68,8)	11 (%36,7)	0,038
Chest pain	14 (%30,4)	7 (%43,8)	7 (%23,3)	0,189
Dyspnea	17 (%34,7)	4 (%25)	13 (%39,4)	0,360
Feeling of happiness	7 (%15,6)	3 (%18,8)	4 (%13,8)	0,686
Increased desire	8 (%17,8)	4 (%25)	4 (%13,8)	0,427
Fatigue	20 (%44,4)	8 (%50)	12 (%41,4)	0,577
Fear of death	16 (%35,6)	4 (%25)	12 (%41,4)	0,272
Dream-like state	18 (%40)	6 (%37,5)	12 (%41,4)	0,799
<b>Physical examination findings</b>				
Hypertension	7 (%14,3)	1 (%6,3)	6 (%18,2)	0,402
Hypotension	8 (%16,3)	2 (%12,5)	6 (%18,2)	1,000

(continued)

Tachycardia	37 (%75,5)	14 (%87,5)	23 (%69,7)	0,290
Respiratory depression	7 (%14,3)	-	7 (%21,2)	0,080
Redness in eyes	33 (%67,3)	11 (%68,8)	22 (%66,7)	0,884
Pupils				0,096
Isochoric	11 (%22,4)	4 (%25)	7 (%21,2)	
miotic	8 (%16,3)	-	8 (%24,2)	
Mydriatic	30 (%61,2)	12 (%75)	18 (%54,5)	
Lateral findings				0,668
Present	7 (%14,3)	3 (%18,8)	4 (%12,1)	
None	42 (%85,7)	13 (%81,3)	29 (%87,9)	
<b>ECG findings</b>				0,514
Normal	10 (%20,4)	3 (%18,8)	7 (%21,2)	
Bradycardia	-	-	-	
Sinus tachycardia	35 (%71,4)	13 (%81,3)	22 (%66,7)	
Negative T wave	2 (%4,1)	-	2 (%6,1)	
ST depression	2 (%4,1)	-	2 (%6,1)	
ST elevation	-	-	-	
<b>Hospitalization</b>				0,020
Hospitalized	10 (%20,4)	-	10 (%30,3)	
Discharged from ED	39 (%79,6)	16 (%100)	23 (%69,7)	
Exitus	3 (%6,1)	-	3 (%9,1)	0,541

\*Chi-square test. Fisher's exact test is used if a cell includes a cell count of less than 5.

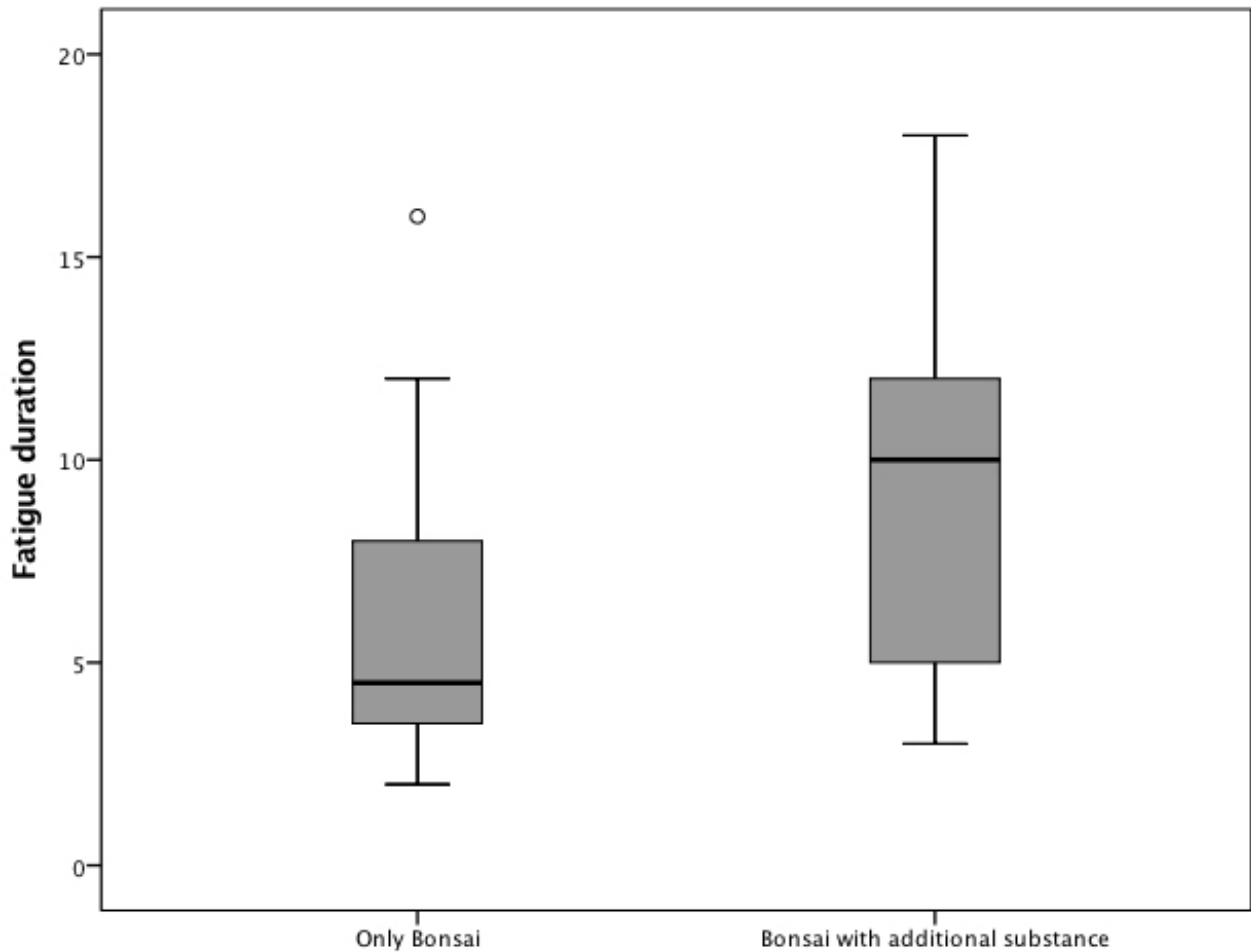
substance was significantly lower ( $p=0,003$ ). The fatigue duration time in Group 2 was significantly higher ( $p=0,010$ ) (Figure 1). The median time to remission of symptoms and median follow-up time of the patients in the ED were 3 hours and 6 hours, respectively. Time to remission of symptoms in Group2 was significantly higher than Group 1 ( $p=0.001$ ) (Table 3, Figure 2).

The reasons for hospitalization of 10 patients in Group 2 were as follows: Respiratory insufficiency ( $n=4$ ), AKI ( $n=1$ ), status epilepticus ( $n=1$ ), PE ( $n=1$ ), ACS ( $n=1$ ) and poor general condition ( $n=1$ ). One patient had suffered cardiopulmonary arrest before admission and died in the ED. While 2 patients who developed respiratory depression hospitalized in the intensive care unit (ICU) died within 48 hours, the other 2 patients were discharged from ICU after a 24– hour follow up. Minor atheroma plaque was detected in the patient hospitalized with the diagnosis of ACS and the patient was also discharged after disappearing of the symptoms.

The patient, whose subsegmental PE was detected on thoracic CT angiography, was discharged after treatment. Dialysis has been used to treat the patient who developed acute renal failure and was discharged with recovery after ICU follow up. The patient who was hospitalized due to seizure in ED was also discharged without recurrence of seizure by recommending polyclinic control. No additional pathology developed after the follow-up of the patients discharged from the ED.

## Discussion

SCs use is a major public health problem among adolescents and young adults, and substance users generally prefer to use many additional substances together (17). There could be many reasons for the intake of a combination of drugs. The main reason is to increase the psychoactive experience and get rid of the side effects of other drugs (18).



**Figure 1.** Comparison of fatigue duration between the groups

**Table 3.** Comparison of patients' vital signs, laboratory levels, and time to remission of symptoms

	<b>Group 1</b>		<b>Group 2</b>	<b>p*</b>
	<b>Total</b>	<b>(n=16)</b>	<b>(n=33)</b>	
	<b>median (min-max)</b>			
<b>Fatigue duration (hours)</b>	8 (2-18)	5 (2-16)	10 (3-18)	<b>0,010</b>
<b>Time to remission of symptoms (hours)</b>	3 (1-48)	3 (1-10)	6 (1-48)	<b>0,001</b>
<b>GCS</b>	12 (3-15)	14 (7-15)	10 (3-15)	<b>0,003</b>
<b>Vital signs</b>				
Systolic blood pressure (mmHg)	120 (80-190)	110 (90-190)	120 (80-190)	0,293
Diastolic blood pressure (mmHg)	70 (50-100)	70 (50-100)	70 (50-100)	0,815
Heart rate (beats/min)	107 (62-147)	108 (82-147)	106 (62-140)	0,272
Respiratory rate	18 (8-28)	18 (16-25)	18 (8-28)	0,155

(continued)

Blood Gases				
sPO2	97 (19-100)	97 (19-100)	96 (62-100)	0,519
pH	7,35 (6,7-739)	7,37 (7,29-739)	7,33 (6,7-7,46)	<b>0,005</b>
pCO2	45,5 (17,1-82)	42,1 (29-50)	48,5 (17,1-82)	<b>0,016</b>
pO2	71,8 (22-202)	92,5 (36,3-97)	65 (22-202)	<b>0,002</b>
Base deficit	2,7 (0-27)	2 (0-6)	3 (0,6-27)	<b>0,024</b>
Lactate	1,95 (0,7-27)	1,65 (0,7-4)	2,2 (0,7-27)	0,115
<b>Ethanol level</b>	114 (0-481)	0 (0-426)	115 (0-481)	0,542
<b>Glucose</b>	100,5 (45-292)	110 (69-292)	95,5 (45-223)	<b>0,019</b>
<b>sodium (mg/mL)</b>	136,5 (126-144)	137 (131-143)	136 (126-144)	0,860

\*Mann-Whitney-U test

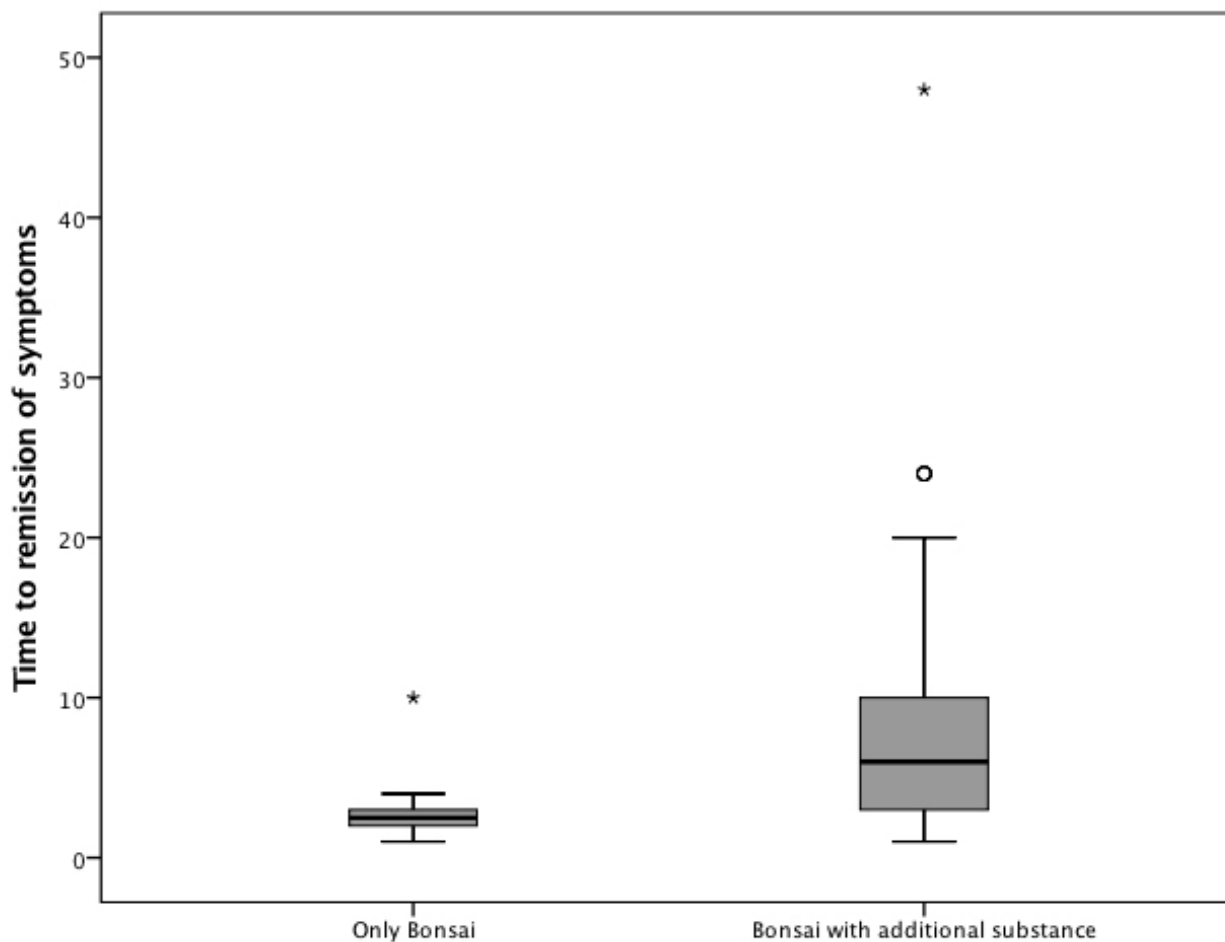


Figure 2. Comparison of the symptom remission times between the groups

In their study on patients using SC, Yalçın et al. (18) reported that the mean age of the patients was  $26.8 \pm 7.5$  years and 92.6% of the patients were male. In another study by Barratt et al. (19), they determined that the average age the patients taking SC was 27 years in Australia and that 77% of users were male. The age and sex ratio in our study was similar to the literature. We believe that the main reason why SCs are preferred by young people is a cheap price. The reason why drug use is more common among men may be due to the fact that men are more independent and spend more time in areas where drug use is more common.

Yilmaz et al. (20). stated that “bonsai” users were mostly primary school graduates. In a study conducted in the United States, it was reported that 11% of high school students had used marijuana (cannabis) or SC in the past year (21). In our study, bonsai users were found to be mostly primary school graduates also. We believe that drug addicts prefer the easily accessible and cheapest drug on the market because of their low education level and low incomes. Wasting time and money on searching for drugs is likely to be a result of a low level of education in drug-users.

The main reasons for the rapid spread of SCs among people may be related to the fact that they look like cannabis, are used in a similar way, were not identified in the toxicological screening tests previously, are easily accessible and cheap (1,22). Although cigarette smoking was found to be the most common way to consume SCs in the studies, other forms of intake such as evaporation, oral or rectal way have also been reported (4,5). Indeed, in our study, it was found that patients had a low level of income, mostly used cannabis before, used SCs for pleasure and in the form of smoking. We believe that the reason for switching to SCs is due to the fact that SCs resemble marijuana in every aspect and are easily accessible and cheaper.

Although SCs give the desired psychoactive effects such as euphoria, anxiety, agitation, irritability, psychosis, and changes in cognitive skills, undesirable effects such as sweating, nausea, vomiting, appetite changes, hypertension/hypotension, chest pain, tachycardia/bradycardia, respiratory depression, confusion, psychomotor agitation, somnolence, and sedation may also be seen (4, 23). The most common physical effect reported after SC intake is tachycardia (23). In their

study on SC users, Barratt et al. reported a decreased motor coordination (39%) and arrhythmias (33%) as the most common developed disorders (19). Forrester reported that the leading symptoms were palpitations and chest pain in 48.5% of patients, followed by dizziness and drowsiness in 24.3% of patients (24). Negative inotropic effect and vasodilator effect of CB1 receptor have been demonstrated (25). In our study, consistent with the literature, the most frequent symptom was palpitation and the most common finding was tachycardia. Being CB1 receptor agonist, we believe that bonsai leads to tachycardia by causing an increase in the amount of dopamine. In addition, it should be kept in mind that additional drug use and additional symptoms such as anxiety and hypotension might lead to an increase in tachycardia by causing hormonal activation.

We could not find any study in the literature comparing the effects of concomitant drug intake along with “bonsai” on symptoms and findings. Although no difference was found regarding symptoms and findings between the groups in our study, the duration of symptoms of the patients with additional drug intake was found to be longer, according to the results of the analysis of the patients included in our study. We think that “bonsai” and concomitant drugs potentiate each other and lead to prolongation of symptom duration and increase in symptom severity, even not changing the frequency of symptoms.

SCs causing respiratory distress and/or respiratory arrest remain unclear (26). In our study, we determined that  $p\text{CO}_2$  values were slightly higher and  $\text{PaO}_2$  was lower and that patients with concomitant drug intake were more acidotic. We believe that the additional drugs affect respiration directly or indirectly and that this effect is greater in patients with additional drug (especially opiates) intake.

Although it is known that symptoms and findings associated with SC intake last less than 8 hours and the patients are discharged, there are also reported patients with symptoms and findings that have lasted longer than 24 hours (27). In our study, the median time to remission of symptoms and median follow-up time were 3 hours and 6 hours, respectively. The duration of symptoms was significantly longer in patients with additional drug intake. Time to remission of symptoms was shorter than 8 hours in accordance with the literature.



Monte et al. (28) reported that 8% of patients in their study were hospitalized. In a study conducted by Küçük et al. (1) in our country, it was determined that 46% of patients were hospitalized. The rate of hospitalization is 20.4% in our study and patients with only “bonsai” intake were found to be completely discharged.

In our study, hospitalized patients were found to have a worse clinical condition. The main reason for higher hospitalization rates in our country might be the presence of a more dangerous “bonsai” group in our country or follow-up hospitalization of patients as the infrastructure of our ED is not suitable for long-term patient follow-up. We believe that the most basic reason for more frequent hospitalization of patients with additional drug intake is a possible potentiation between bonsai and other drugs and/or the effects of other drugs. Also, it should be noted that the effect generated by bonsai might strengthen the side effects of other drugs.

In conclusion, the interaction between “bonsai” and other drugs is not entirely clear. Therefore, additional drugs should be questioned in patients with “bonsai” intake and health staff should be more careful during follow-up and treatment processes of patients with additional drug intake.

### Limitation

In the literature, many studies on bonsai are retrospective and do not use diagnostic tests. Our study was prospective and verified by diagnostic tests, and it was the first study in the literature that compared the “bonsai” intake group with the “bonsai” group with additional drugs intake. Although significant results have been revealed, our study has some limitations. First, our study is a single-center study., The second limitation is the small number of cases, and the last limitation is the lack of very large diagnostic test panels.

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the article. MK is responsible for data analysis. AI contributed to data acquisition.

**Informed consent:** All patients provided written informed consent prior to study participation.

**Ethical approval:** This study was initiated in the ED of a tertiary hospital following ethics committee approval.

**Human rights:** Our work does not infringe on any rights of others, including privacy rights, and intellectual property rights. There is no human rights violation in our manuscript.

**Conflicts of interest:** Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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