Characteristics of Synthetic Cannabinoid and Cannabis Users Admitted to a Psychiatric Hospital: A Comparative Study

Nadav Shalit, MD[a,b,‡,*]; Ran Barzilay, MD, PhD[a,b,c,‡]; Gal Shoval, MD[a,b]; Dan Shlosberg, MD, PhD[a,b]; Nofar Mor[a]; Nofar Zweigenhaft[a]; Abraham Weizman, MD[a,b,c]; and Amir Krivoy, MD[a,b,c]

ABSTRACT

Background: Psychotic and affective exacerbations associated with synthetic cannabinoid (SC) use are becoming an emerging concern in psychiatric hospitals. However, data are lacking regarding whether clinical manifestations of SC use differ from those associated with cannabis use.

Objective: Our aim was to explore the unique profile of SC users admitted to a mental health center in terms of demographic, clinical, and physiologic variables in comparison to cannabis users.

Methods: We retrieved retrospective data of patients admitted to a mental health center between October 2007 and May 2014 who self-reported recent use of SC (n = 60) and patients who were cannabis users (positive carboxy-tetrahydrocannabinol urine test at admission) without a history of SC use (n = 163). Clinical measures included hospitalization length, number of previous hospitalizations, Positive and Negative Syndrome Scale (PANSS) scores, psychiatric status at admission, and relevant physiologic and laboratory parameters.

Results: Hospitalized SC users were younger than hospitalized cannabis users (n = 163) (30.46 ± 7.83 years versus 34.67 ± 10.07 years, $U_{223} = 3{,}781.5$, $P = .009$, respectively). SC patients had longer hospitalizations compared to cannabis users (43.45 ± 54.02 days versus 22.91 ± 31.36 days, $U_{219} = 5{,}701.5$, $P = .005$, respectively), had more previous hospitalizations (3.73 ± 5.05 versus 1.98 ± 5.12, $U_{223} = 6{,}284$, $P < .001$, respectively), and were more likely to be hospitalized by criminal court order (36.7% [n = 22] versus 19.9% [n = 32], $\chi^2_2 = 7.136$, $P = .028$, respectively). SC patients presented with a more severe clinical picture manifested by higher total PANSS scores (82.53 ± 23.05 versus 69.98 ± 19.94, $t_{91} = -2.696$, $P = .008$) in a subset of patients with PANSS scores assessed within a week from admission (n = 30 in the SC group and n = 63 in the cannabis group). No differences were found in physiologic or laboratory measures on admission between the SC and cannabis groups.

Conclusions: Patients admitted following use of SC are generally younger males who have higher severity of psychotic symptoms at admission, are more likely to be admitted by criminal court order, and require longer hospitalization periods in comparison to cannabis users.

J Clin Psychiatry 2016;77(8):e989–e995
dx.doi.org/10.4088/JCP.15m09938

[a]Geha Mental Health Center, Petach-Tikva, Israel
[b]Sackler Faculty of Medicine, Tel Aviv University, Israel
[c]Felsenstein Medical Research Center, Petach-Tikva, Israel
‡Drs Shalit and Barzilay contributed equally to this work.
**Corresponding author:* Nadav Shalit, MD, Geha Mental Health Center and Sackler Faculty of Medicine, Tel Aviv University, 1 Helsinki St, Petach-Tikva, 49100, Israel (nashke@gmail.com).

Since the early 2000s, various synthetic cannabinoids (SC) have been developed as designer drugs for recreational use. They have become popular worldwide as "legal highs," owing mainly to lack of routine detection methods and undetermined legal status. The SC, sold under various trade names including "Spice," "K2," "Aroma," and "Mr. Nice Guy,"[1] were originally developed by researchers attempting to characterize the endocannabinoid system as well as find potential novel therapeutics.[2]

The majority of SC used as recreational drugs have higher affinity to the cannabinoid CB_1 receptor than Δ^9-tetrahydrocannabinol (THC), the primary psychoactive molecule in cannabis. Furthermore, THC is a partial agonist at the CB_1 receptor, while SC are generally full agonists of this receptor (Table 1). As opposed to natural cannabis products, SC lack other plant-derived cannabinoid molecules (phytocannabinoids) such as cannabidiol, cannabigerol, Δ^9-tetrahydrocannabivarin, cannabidivarin, and Δ^9-cannabichromene. These phytocannabinoids are known to modulate the endocannabinoid system by various mechanisms such as CB_1 and CB_2 agonism and antagonism; inhibition of endocannabinoid synthesizing and degrading enzymes such as fatty acid amide hydrolase, diacylglycerol lipase, and monoacylglycerol lipase; agonist and antagonist activity at serotonergic and adrenergic receptors; and activation of ion channels including transient receptor potential channels such as TRPV1 and TRPV2.[3,4]

Cannabidiol, in particular, is suggested to have some antipsychotic and anxiolytic properties, presumably related to its unique activity as a modulator of the endocannabinoid system.[5–8]

In addition to synthetic cannabinoids, recreational SC products may contain a variety of other psychoactive substances. The active SC compound is usually dissolved in an organic solvent in which an herbal ingredient is later soaked. Although generally the herbal ingredient is inert, some products were found to use psychoactive herbs such as *Leonotis leonurus* and *Pedicularis densiflora*.[1] Oleamide, a fatty acid derivative with cannabinoid-like activity, has been reportedly found frequently in recreational SC products.[9] Opioids such as *O*-desmethyltramadol and mitragynine (a μ-opioid agonist found in the plant *Mitragyna speciosa*) were identified in a recreational SC product named "Krypton," which was linked to 9 unintentional deaths in users.[10] Many other psychoactive substances have been identified in various recreational SC products over recent years—the mixture of

Clinical Points

- In recent years, there is an increasing use of synthetic cannabinoids as recreational drugs, but literature regarding their psychoactive effects is limited.
- If a patient presents with severe psychotic symptoms coupled with aggressive behavior, synthetic cannabinoid use should be considered.
- Synthetic cannabinoid use is more prevalent in younger age groups that are especially prone to the deleterious psychiatric effects of cannabinoids.

different substances with recreational SC products is ever-changing, lending to unpredictable pharmacodynamic and pharmacokinetic interactions.[1]

In recent years, several case reports and case series have been published regarding the clinical effects of SCs. The main findings emerging from these reports indicate physiological and psychoactive effects differing notably from those of cannabis. These include a more pronounced psychoactive effect and serious potential adverse effects[5] including acute renal failure,[11] cerebrovascular accidents,[12] seizures,[13] psychosis,[14,15] and pronounced withdrawal phenomena.[16] For more information regarding SC-related clinical effects, we refer the reader to the systematic review by Papanti et al.[17] Recently, a rise in emergency room visits in the United States after SC consumption has been reported,[18–20] and a recent large-scale global survey has shown that when compared to cannabis users, SC users have a 30-fold higher relative risk of seeking emergency medical care and report significantly more symptoms including panic, anxiety, paranoia, agitation, and hallucinations.[21,22]

Based on previous research in this area, we hypothesized that psychiatric hospitalizations following SC use will be characterized by a more severe clinical picture when compared to hospitalizations following cannabis use. In the present study, our aim was to identify clinical, sociodemographic, and physiologic parameters differentiating SC and cannabis users, in an attempt to characterize the unique clinical impact of SC use. This, we believe, may aid in bridging the gap of knowledge regarding the clinical implications of synthetic cannabinoid use.

METHODS

We used the electronic medical records system of Geha Mental Health Center (GMHC), a large, regional mental health center with a catchment area of approximately 600,000 inhabitants. We retrieved data on all hospitalized patients between October 2007 and May 2014 (n = 4,188). The GMHC review board approved the study. The need for informed consent was waived by the committee due to the retrospective nature of the study.

Population

Using the keywords *synthetic cannabinoids* and other street names of synthetic cannabinoids used in Israel, we identified patients who potentially used SC. We then reviewed their hospitalization record to confirm their self-report of SC use prior to hospitalization. The control group (cannabis users) was retrieved using the inclusion criteria of positive carboxy-tetrahydrocannabinol urine test at admission without a recent or past SC use during the same 7-year duration. The medical records of all participants were evaluated thoroughly by a psychiatrist (N.S. or R.B.).

Variables

We retrieved demographic data including age at admission, marital and educational status, and gender. The clinical data included presence of psychotic and affective symptoms at admission, legal status at admission (consent, civil commitment, or court order—after committing a violent crime and deemed unfit to stand trial), history of substance use, Positive and Negative Syndrome Scale (PANSS)[23] total score and subscores at admission, length of index hospitalization, number of previous hospitalizations, and primary psychiatric diagnosis at discharge (of index admission) established by *DSM-IV-TR* criteria. Diagnosis was established according to *DSM-IV-TR* criteria by the patient's case manager after a review by the ward's multidisciplinary team and by the ward's director.

Physiologic parameters included heart rate, blood pressure, and temperature as routinely measured at admission. Laboratory data included blood tests routinely performed at admission: white blood cell count, serum creatinine, serum urea, aspartate aminotransferase alanine aminotransferase, γ-glutamyl transpeptidase, and creatine kinase.

Statistical Analysis

We used SPSS v. 21 (SPSS Inc, Chicago, Illinois) for statistical analysis. Descriptive statistics are expressed as mean ± SD or rate (%). Two groups of patients were compared: (1) SC group—patients admitted to GMHC who had self-reported recent (within a month prior to admission) use of SC and (2) cannabis group—patients admitted to GMHC with a positive carboxy-tetrahydrocannabinol urine test who had no record of SC use according to the electronic medical record. For univariate analyses, we used 2-tailed Student *t* tests, Mann-Whitney *U* test, χ^2 test, and Fisher exact test, as appropriate. Multivariate analysis was performed using binary logistic regression analyses with type of drug used (SC or cannabis) as a dependent variable controlling for the demographic and clinical variables as covariates. All results are expressed as rates or mean ± SD. A P value $< .05$ was considered to indicate statistical significance.

RESULTS

The total study population, which consisted of 223 patients admitted to GMHC, was divided into 2 groups: patients reporting using SC (n = 60) within the last month prior to admission (of which 86.7%, n = 52, reported SC use within 1 week prior to admission) and patients who used cannabis, who were found positive for THC on a urine

Table 1. Cannabinoid Receptor Binding Affinity of Δ⁹-THC and Representative Synthetic Cannabinoids[a]

Compound	Family/Group	Agonist Activity	Binding Affinity for CB_1 K_i (nM)	Binding Affinity for CB_2 K_i (nM)	THC/SC CB_1 K_i
Δ⁹-THC	Naturally occurring dibenzopyran	Partial agonist	40.7	36.4	1
AB-FUBINACA	Indazole carboxamide	Full agonist	0.9	—	45.6
ADB-FUBINACA	Indazole carboxamide	Full agonist	0.4	—	103
AM2201	Naphthoylindoles	Full agonist	1.0	2.6	40
AM694	Benzoylindoles	Full agonist	0.1	1.4	410
CP-47,497	Cyclohexylphenol	Full agonist	2.2	—	18.6
HU-210	Dibenzopyrans	Full agonist	0.2	0.4	205
JWH-018	Naphthoylindoles	Full agonist	9	2.9	4.6
JWH-073	Naphthoylindoles	Full agonist	8.9	38	4.6
JWH-122	Naphthoylindoles	Full agonist	0.69	1.2	58.6
JWH-250	Phenylacetylindole/benzoylindole	Full agonist	11	33	3.7
UR-144	Tetramethylcyclopropyl indoles	Full agonist	29.0	4.5	1.4
WIN55,212–2	Aminoalkylindoles	Full agonist	62.3	3.3	0.7

[a]Adapted with permission from Castaneto et al.[37]

Abbreviations: AB-FUBINACA = [N-[(2S)-1-Amino-3-methyl-1-oxo-2-butanyl]-1-(4-fluorobenzyl)-1H-indazole-3-carboxamide]; ADB-FUBINACA = [N-(1-Amino-3,3-dimethyl- 1-oxobutan-2-yl)-1-(4-fluorobenzyl-1H-indazole-3-carboxamide]; AM679 = [1-Pentyl-3-(2-iodo-benzoyl)indole]; AM694 = [1-(5-Fluoropentyl)-3-(2-iodobenzoyl)indole]; AM2201 = [N-(5-fluoropentyl)-3–1(-napthoylindole)]; CP47,497 = [2-[(1S,3S)-3-Hydroxycyclohexyl]-5-(2-methyloctan-2-yl) phenol];HU-210 = [(6aR)[-trans-3-(1,1-Dimethylheptyl)-6a,7,10,10a-tetrahydro-1-hydroxy-6,6-dimethyl-6Hdibenzo[b,d] pyran-9-methanol]]; JWH-018 = [Naphthalen-1-yl(1-pentyl-indol-3-yl)methanone]; JWH-073 = [N-Butyl-3-(1-naphthoyl) indole]; JWH-122 = [1-Pentyl-3-(1-(4-methylnaphthoyl))indole]; JWH-250 = [1-Pentyl-3-(2-methoxy-phenylacetyl) indole]; THC = (delta-9-tetrahydrocannabinol); UR-144 = [1-Pentylindol-3-yl)-(2,2,3,3-tetramethylcyclopropyl) methanone]; WIN55,21202 = [2,3-Dihydro-5-methyl-3-(4-morpholinylmethyl)pyrrolo[1,2,3-de]-1,4-benzoxazin-6-yl]-1-napthalenylmethanone.

toxicology screen upon admission and who had no reported use of SC in their past (n = 163). However, it is unclear whether these numbers represent the actual number of SC or cannabis users in our hospitalized patients due to the retrospective nature of the study.

A majority of SC users were also positive for THC on urine toxicology (73.3%, n = 44). Demographic and clinical characteristics of the study population and comparison between the study groups are presented in Table 2. As shown, SC patients were of younger age at the time of admission compared to the cannabis group (30.46 ± 7.83 years versus 34.67 ± 10.07 years, $U_{223} = 3{,}781.5$, $P = .009$) and were less likely to be married (5% versus 19.3%, Fisher exact test: $P = .01$, odds ratio [OR] = 0.22 [95% CI, 0.066–0.76]). No significant differences were observed in gender, education, or occupational status. Comparison of clinical characteristics revealed that SC users were hospitalized for longer periods than cannabis users (43.45 ± 54.02 days versus 22.91 ± 31.36 days, $U_{219} = 5{,}701.5$, $P = .005$, respectively) and had more previous hospitalizations (3.73 ± 5.05 versus 1.98 ± 5.12, $U_{223} = 6{,}284$, $P < .0001$, respectively). SC patients were more likely to be hospitalized compulsorily by a court order (36.7% court order in SC users versus 19.9% court orders in cannabis users, $\chi^2_2 = 7.136$, $P = .028$). SC users were more likely to use cocaine than cannabis users (6.8% versus 0.6%, respectively, Fisher exact test: $P = .02$, OR = 11.78 [95% CI, 1.29–107.73]) and less likely to use hallucinogens (0.0% versus 4.3%, respectively, Fisher exact test: $P < .0001$, OR = 46.71 [95% CI, 2.62–832.40]). Rates of all other substances used were not significantly different between the 2 groups (including alcohol, hypnotics, opiates, other stimulants, and polydrug use).

SC users were significantly less likely to be diagnosed with bipolar disorder when compared to cannabis users (6% versus 22%, respectively, Fisher exact test: $P = .01$, OR = 0.25 [95% CI, 0.09–0.74]). Rates of other psychiatric diagnoses were not significantly different between the two groups.

No differences were observed in the rates of major psychiatric diagnoses using *DSM-IV-TR* criteria (Table 2). About two-thirds of patients met criteria for psychosis on admission, in both groups. However, SC patients had a lower rate of manic symptoms at admission (40% versus 63.2%, $\chi^2_2 = 16.327$, $P < .0001$, respectively).

We compared the PANSS scores for a subset of patients (n = 30 in the SC group and n = 63 in the cannabis group) for whom a PANSS score was available within the first week after admission. The subgroup of patients with available PANSS score did not differ significantly in demographic and clinical characteristics from the group as a whole. SC users had significantly higher total PANSS scores compared to cannabis users (82.53 ± 23.05 versus 69.98 ± 19.94, $t_{91} = -2.696$, $P = .008$, respectively). SC users also had significantly higher positive PANSS subscale scores (22.33 ± 6.84 versus 19.21 ± 7.09, $t_{91} = -2.010$, $P = .047$) and significantly higher negative PANSS subscale scores (18.93 ± 7.74 versus 15.3 ± 6.66, $U_{93} = 1{,}209$, $P = .03$). No statistically significant difference was found in the PANSS depression subscale (8.83 ± 3.475 versus 7.65 ± 3.629, $U_{93} = 1{,}163$, $P = .71$). A subgroup analysis comparing PANSS scores only in patients diagnosed with a psychotic disorder (ie, schizophrenia, schizoaffective disorder, other psychotic disorders, and bipolar disorder) revealed a significantly higher total PANSS score in the SC group when compared to the cannabis group (83.4 ± 22.71 versus 70.63 ± 20.47 respectively, $t = -2.49$, $P = .015$).

Subgroup analysis within the SC user group, comparing SC users without and with concomitant cannabis use, revealed significantly higher total PANSS scores (99.29 ± 15.11 versus 77.43 ± 22.84, $t_{28} = 2.363$, $P = .025$, respectively) and

Table 2. Demographic and Clinical Characteristics of Synthetic Cannabinoid and Cannabis Users

Variable	SC (n = 60)	Cannabis (n = 163)	Test	*t*/*U*/Pearson χ^2	*P* Value	OR (95% CI)
Demographic						
Age, mean (SD), y	30.46 (7.83)	34.67 (10.07)	Mann-Whitney	3,781.5	.009	
Gender male, % (n)	86% (52)	80% (131)	χ^2	−1.182	.188	
Education, mean (SD), y	11.3 (2.07)	11.24 (2.8)	Mann-Whitney	4,215	.774	
Marital status, married, % (n)	5% (3)	19% (31)	Fisher exact		.01	0.22 (0.065–0.76)
Occupational status, employed, % (n)	22% (13)	31% (52)	χ^2	−1.999	.105	
Clinical measures at index admission						
Length of hospitalization, mean (SD), d	43.45 (54.02)	22.91 (31.36)	Mann-Whitney	5,701.5	.005	
Psychotic symptoms at admission, % (n)	66% (40)	67% (110)	χ^2	−0.13	.515	
Mood status at admission, % (n)			χ^2	−16.327	< .0001	
Euthymic	40% (24)	15% (25)				
Manic symptoms	40% (24)	63% (103)				
Dysphoric symptoms	20% (12)	21% (35)				
No. of previous hospitalizations, mean (SD)	3.73 (5.05)	1.98 (5.12)	Mann-Whitney	6,284	< .0001	
PANSS scores within a week from admission, mean (SD)[a]						
Total PANSS	82.53 (23.05)	69.98 (19.94)	*t*	−2.696	.008	
PANSS Positive	22.33 (6.84)	19.21 (7.09)	*t*	−2.01	.047	
PANSS Negative	18.93 (7.74)	15.3 (6.66)	Mann-Whitney	1,209	.03	
PANSS Depression	8.83 (3.48)	7.65 (3.63)	Mann-Whitney	1,163	.71	
Major psychiatric diagnosis (rate between groups), % (n)						
Schizophrenia	28% (17)	25% (42)	Fisher exact		.73	1.14 (0.59–2.21)
Other psychotic	16% (10)	12% (20)	Fisher exact		.38	1.43 (0.63–3.26)
Schizoaffective	16% (10)	8% (14)	Fisher exact		.09	2.13 (0.89–5.09)
Bipolar	6% (4)	22% (36)	Fisher exact		.01	0.25 (0.09–0.74)
Personality disorders	15% (9)	16% (26)	Fisher exact		1.0	0.93 (0.41–2.12)
Legal status on admission, % (n)			χ^2	−7.136	.028	
Consent	43% (26)	49% (81)				
Civil commitment	20% (12)	31% (50)				
Court order (criminal)	37% (22)	20% (32)				
Other substance use, % (n)						
No other substance use	40% (24)	53% (86)	χ^2	2.31	.13	0.60 (0.33–1.10)
Alcohol	22% (13)	11% (19)	χ^2	2.81	.09	2.10 (0.96–4.57)
Opiates	0.0% (0)	2.5% (4)	Fisher exact		.58	0.30 (0.02–5.62)
Benzodiazepines	3.4% (2)	0.6% (1)	Fisher exact		1.0	1.39 (0.12–15.61)
Cocaine	6.8% (4)	0.6% (1)	Fisher exact		.02	11.78 (1.29–107.73)
Hallucinogens	0.0% (0)	4.3% (7)	Fisher exact		< .0001	46.71 (2.62–832.40)
Amphetamines/other stimulants	1.7% (1)	1.8% (3)	Fisher exact		1.0	0.92 (0.09–9.02)
Polydrug use	22% (13)	25.2% (41)	χ^2	0.13	.72	0.82 (0.41–1.67)

[a]For PANSS scores: SC users, n = 30; cannabis users, n = 63.
Abbreviations: OR = odds ratio, PANSS = Positive and Negative Syndrome Scale, SC = synthetic cannabinoids.

negative PANSS scores (26.29 ± 5.41 versus 16.7 ± 6.96, $t_{28} = 3.335$, $P = .002$, respectively), but not positive PANSS scores (26.57 ± 2.99 versus 21.04 ± 7.19, $t_{28} = 1.964$, $P = .06$, respectively) in SC-only users compared to SC users with concomitant cannabis use.

No other significant demographic, clinical, or physiological differences were found between these subgroups. Table 3 presents a comparison of physiologic and laboratory tests at admission between the study groups. We found no differences in heart rate, blood pressure, body temperature, white blood cell counts, creatinine and urea serum levels, liver enzymes, or creatine kinase between study groups.

Multivariate analysis was performed by a binary logistic regression to assess the impact of several factors on the likelihood of patients belonging to either the SC or cannabis user groups. The model contained 3 independent variables that were found to be significantly different between groups in the univariate analysis (age, total length of hospitalization, and total PANSS score during the first week of hospitalization). The full model containing all potential predictors was statistically significant ($\chi^2_3 = 17.196$, N = 223, $P = .001$), indicating that the model was able to distinguish between SC and cannabis users. The model as a whole explained between 23.7% (Cox and Snell R^2) and 33.2% (Nagelkerke R^2) of the variance in cannabinoid use (either SC or cannabis) and correctly classified 79.6% of cases. All 3 independent variables made a unique statistically significant contribution to the model, controlling for all other factors in the model—age at admission ($\beta = -0.79$, $P = .024$), PANSS score during first week of hospitalization ($\beta = .028$, $P = .029$), and total duration of hospitalization ($\beta = .013$, $P = .036$). Inclusion of substance use other than cannabinoids as a covariate revealed that specific substance use did not affect the model significantly. Legal status was not included in the model since it was highly intercorrelated with length of hospitalization. A complementary binary logistic regression containing age, PANSS score during first week of hospitalization, and legal status as independent variables indicated significant contributions for age and total PANSS score, similar to those shown in the first model. Legal status contributed significantly to the model (SC versus cannabis: admission by criminal court order versus consent, adjusted OR = 5.406 [95% CI, 1.4–20.8], $P = .014$).

Table 3. Physiologic and Laboratory Measures of Synthetic Cannabinoid and Cannabis Users

Variable	SC (n = 60)	Cannabis (n = 163)	Test	*t*/*U*/Pearson χ^2	*P* Value
Physiologic measures at admission					
Heart rate, mean (SD) BPM	88.6 (16.4)	88.12 (15.6)	*t*	–0.2	.842
Tachycardia, BPM > 100, % (n)	26% (16)	23% (38)	χ^2	–0.445	.309
Hypertension (Sys > 140 or Dia > 100 mm Hg), % (n)	18% (11)	14% (23)	χ^2	–0.702	.403
Body temperature, mean (SD) °C	36.52 (0.32)	36.59 (0.32)	Mann-Whitney	3,679	.259
Laboratory tests at admission					
WBC, mean (SD) K/μL	9,566 (2,709)	9,294 (2,868)	Mann-Whitney	4,626	.528
Creatinine, mean (SD) mg/dL	0.824 (0.126)	0.814 (0.185)	Mann-Whitney	3,856	.605
Urea, mean (SD) mg/dL	25.53 (7.2)	26.77 (8.64)	Mann-Whitney	3,522.5	.663
AST, mean (SD) U/L	31.67 (32.82)	32.68 (27.98)	Mann-Whitney	4,002	.570
ALT, mean (SD) U/L	27.54 (34.7)	30.88 (33.65)	Mann-Whitney	3,674.5	.153
GGT, mean (SD) U/L	28.95 (20.1)	34.07 (31.32)	Mann-Whitney	3,811.5	.285
CK, mean (SD) U/L	384.75 (607)	508.45 (1290)	Mann-Whitney	3,355	.588

Abbreviations: ALT = alanine aminotransferase, AST = aspartate aminotransferase, BPM = beats per minute, CK = creatine kinase, Dia = diastolic blood pressure, GGT = γ-glutamyl transpeptidase, SC = synthetic cannabinoids, Sys = systolic blood pressure, WBC = white blood cell count.

DISCUSSION

In this study, we compared several clinical, sociodemographic, and physiologic parameters between 2 groups of patients admitted to a single mental health center in Israel—one consisting of hospitalized patients who self-reported use of synthetic cannabinoids 1 month prior to hospitalization and the other of patients hospitalized with documented use of cannabis (confirmed by urine toxicology at admission). To our knowledge, this is the first study comparing clinical characteristics of these 2 patient groups. Our finding that over 73% of SC users also use cannabis matches previous reports on the subject[22] and highlights the importance of comparing SC users to cannabis users.

We found that SC users were predominantly younger men, most of whom were admitted due to a psychotic exacerbation. When compared to the cannabis user group, the clinical manifestations were more severe, as demonstrated by a higher PANSS score at admission and the need for longer hospitalizations. Moreover, although about 60% of the 2 groups had been involuntarily admitted, SC users had higher rates of admission under a criminal court order.

A recent report by the US Substance Abuse and Mental Health Services Administration has shown a similar male preponderance of SC users and a sharp rise in emergency room visits of SC users between the ages 12–20 years in recent years.[20] In a survey conducted in Israel among 16- to 18-year-old high school students in 2011, 3.5% reported use of SC in the past year (males, 5.2%; females, 1.7%), while 9.6% reported SC use by peers (males, 12.6%; females, 6.6%).[24] Evidence suggests that early exposure to THC is a risk factor for the development of serious psychiatric disorders.[25–27] In addition, previous studies have shown that recreational SC products may contain several other psychoactive compounds. Our finding of a younger mean age of SC users may indicate that this age group is at an increased risk, since it seems likely that SC use may lead to a worse psychosis and poorer prognosis compared to cannabis use.

Our findings that significantly more SC users were admitted by criminal court order and had longer periods of hospitalizations and a higher PANSS score may suggest that SC users tend to behave more aggressively. Previous research exploring a possible link between the endocannabinoid system and aggressive behavior produced inconsistent results.[28–30] Our findings emphasize the need for further research regarding the association between the endocannabinoid system and aggressive behavior.

Contrary to several case studies published in recent years that described physiologic alterations and adverse effects linked to SC use,[5,11–16] none of the physiologic parameters studied were significantly different between the 2 groups. It is reasonable to assume that physiologic effects are more pronounced during acute intoxication, but owing to the retrospective nature of the study, we were unable to determine if subjects were indeed acutely intoxicated at time of admission. Thus, our negative findings may stem from the absence of SC intoxication at admission. These negative findings may also be attributed to the fact that SC users were compared to cannabis users, and any difference from baseline may be minimized by similar changes in cannabis users. It is of note that previous case reports referred to series of patients all using the same SC compound. In our study, we were unable to differentiate between the various SC compounds; thus, any unique physiologic effect of a specific SC compound might have been concealed by data from users of other SC compounds.

An unexpected finding was that of a higher percentage of manic symptoms in the cannabis group compared to the SC group. One possible explanation is the significantly higher rate of bipolar disorder in our group of cannabis users. Another possible explanation for this observation is that the increased severity of psychotic symptoms (as assessed by the PANSS) in the SC group might obscure the affective symptoms. This finding merits further study regarding the effects of SC on affective symptomatology.

As mentioned before, most SC have a more potent agonistic activity at the CB_1 receptor compared to THC and are full agonists at the CB_1 receptor compared to

THC, which is a partial agonist. Moreover, all of the SC lack cannabidiol and other phytocannabinoids found in cannabis[1] and may contain several other, noncannabinoid psychoactive compounds. Studies in recent years have shown that cannabis strains with a higher THC/cannabidiol ratio have a higher potential of inducing psychotic symptoms in susceptible individuals.[31–33] These findings have led researchers to hypothesize that cannabidiol may have antipsychotic activity. Indeed, several studies have shown that cannabidiol exhibits antipsychotic and anxiolytic properties.[31,34,35] Leweke et al have shown that when given to schizophrenia patients, cannabidiol shows antipsychotic activity comparable to that of the second generation antipsychotic drug amisulpride.[36] Thus, SC's high affinity to the CB_1 receptor, its lack of the putative protective effect of cannabidiol, and the effects of other noncannabinoid psychoactive compounds found in recreational SC products may be involved in the increased severity of psychotic symptoms and relative resistance to antipsychotic treatment (reflected by longer duration of hospitalization) seen in SC users in our study. Furthermore, SC users with concomitant cannabis use displayed lower psychotic severity compared to SC users without concomitant cannabis use, supporting the notion that the presence of cannabidiol in cannabis may have some protective effect with regard to psychosis.

A major limitation of this study is that the SC patient group is composed of patients who self-reported SC use. Although several kits able to identify urine metabolites of common SC compounds are available today, none are currently in routine use in Israeli hospitals. Other limitations of our study are the use of retrospectively collected data, reliance on electronic medical records that are prone to data omission, and the fact that data were collected from a single hospital, which leads to an inherent bias as it represents only the population residing in the catchment area. Generalization of our findings to all SC users should be done cautiously, as we studied only SC users who had been hospitalized in a mental health center. A possible cause for the difference between the 2 study groups is that SC users consume a higher dose of CB_1 agonists. Unfortunately, we had no way of determining the dosage of substances used by either of the study groups.

The major strength of our study is the relatively large number of SC users and the use of a comparative group of established cannabis users (according to positive urine THC results at admission). The use of this control group allows us to identify the unique impact of SC use on the measured variables, since, as shown in this and previous studies,[37] a majority of SC users also use cannabis.

CONCLUSION

The findings of this study indicate that SC users are younger, have more severe psychotic symptoms, have higher rates of aggressive behavior (as reflected by higher rates of hospitalizations by court order), and require longer hospitalization for stabilization compared to cannabis users. These differences may be attributed, at least in part, to the higher potency of SC at the CB_1 receptor and lack of the moderating effect of cannabidiol in SC leading to unbalanced overstimulation of the endocannabinoid system. The finding of worse psychosis following SC use complements the substantial literature linking cannabis use to the emergence and exacerbation of psychotic disorders.

Further studies are needed to replicate these findings and to gain a more accurate clinical picture of the effect of SC in hospitalized as well as nonhospitalized individuals. This may be done by examining larger populations that include SC users who are not psychiatric patients and focusing on differentiating specific SC compounds, thoroughly characterizing both their physiologic and psychoactive effects. This study raises concern regarding the long-term effect of SC use in young people, especially the risk for developing psychotic and aggressive symptoms. Further studies on the possible role of cannabidiol as a targeted treatment for SC-induced psychosis are warranted.

Submitted: March 4, 2015; accepted August 18, 2015.

Online first: July 5, 2016.

Potential conflicts of interest: The authors declare no conflict of interest.

Funding/support: None.

REFERENCES

1. Fattore L, Fratta W. Beyond THC: the new generation of cannabinoid designer drugs. *Front Behav Neurosci*. 2011;5:60.
2. Pertwee RG. Cannabinoid pharmacology: the first 66 years. *Br J Pharmacol*. 2006;147(suppl 1):S163–S171.
3. Hill AJ, Williams CM, Whalley BJ, et al. Phytocannabinoids as novel therapeutic agents in CNS disorders. *Pharmacol Ther*. 2012;133(1):79–97.
4. Pertwee RG. The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: delta9-tetrahydrocannabinol, cannabidiol and delta9-tetrahydrocannabivarin. *Br J Pharmacol*. 2008;153(2):199–215.
5. Spaderna M, Addy PH, D'Souza DC. Spicing things up: synthetic cannabinoids. *Psychopharmacology (Berl)*. 2013;228(4):525–540.
6. Annual Report on the Implementation of Council Decision 2005/387/JHA. European Monitoring Centre for Drugs and Drug Addiction Web site. http://www.emcdda.europa.eu/html.cfm/index132901EN.html. 2008. Accessed October 16, 2014.
7. Radhakrishnan R, Wilkinson ST, D'Souza DC. Gone to pot—a review of the association between cannabis and psychosis. *Front Psychiatry*. 2014;5:54.
8. Zuardi AW, Crippa JA, Hallak JE, et al. A critical review of the antipsychotic effects of cannabidiol: 30 years of a translational investigation. *Curr Pharm Des*. 2012;18(32):5131–5140.
9. Dresen S, Ferreirós N, Pütz M, et al. Monitoring of herbal mixtures potentially containing synthetic cannabinoids as psychoactive compounds. *J Mass Spectrom*. 2010;45(10):1186–1194.
10. Kronstrand R, Roman M, Thelander G, et al. Unintentional fatal intoxications with mitragynine and O-desmethyltramadol from the herbal blend Krypton. *J Anal Toxicol*. 2011;35(4):242–247.
11. Centers for Disease Control and Prevention (CDC). Acute kidney injury associated with synthetic cannabinoid use—multiple states, 2012. *MMWR Morb Mortal Wkly Rep*. 2013;62(6):93–98.
12. Freeman MJ, Rose DZ, Myers MA, et al. Ischemic stroke after use of the synthetic marijuana "spice." *Neurology*. 2013;81(24):2090–2093.
13. Schneir AB, Baumbacher T. Convulsions associated with the use of a synthetic cannabinoid product. *J Med Toxicol*. 2012;8(1):62–64.
14. Every-Palmer S. Synthetic cannabinoid JWH-018 and psychosis: an explorative study. *Drug Alcohol Depend*. 2011;117(2–3):152–157.
15. Durand D, Delgado LL, de la Parra-Pellot DM, et al. Psychosis and severe rhabdomyolysis associated with synthetic cannabinoid use: a case report. *Clin Schizophr Relat Psychoses*. 2015;8(4):205–208.
16. Zimmermann US, Winkelmann PR, Pilhatsch M,

et al. Withdrawal phenomena and dependence syndrome after the consumption of "spice gold." *Dtsch Arztebl Int*. 2009;106(27):464–467.
17. Papanti D, Schifano F, Botteon G, et al. "Spiceophrenia": a systematic overview of "spice"-related psychopathological issues and a case report. *Hum Psychopharmacol*. 2013;28(4):379–389.
18. Bronstein AC, Spyker DA, Cantilena LR Jr, et al. 2011 annual report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 29th annual report. *Clin Toxicol (Phila)*. 2012;50(10):911–1164.
19. Hoyte CO, Jacob J, Monte AA, et al. A characterization of synthetic cannabinoid exposures reported to the National Poison Data System in 2010. *Ann Emerg Med*. 2012;60(4):435–438.
20. Bush DM, Woodwell DA. *Update: Drug-Related Emergency Department Visits Involving Synthetic Cannabinoids*. http://www.ncbi.nlm.nih.gov/books/NBK350768/#SR-188_RB-2047.s. Rockville, MD: Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality; October 16, 2014.
21. Sadhasivam S, Zhang X, Chidambaran V, et al. Novel associations between FAAH genetic variants and postoperative central opioid-related adverse effects. *Pharmacogenomics J*. 2015;15(5):436–442.
22. Winstock AR, Barratt MJ. Synthetic cannabis: a comparison of patterns of use and effect profile with natural cannabis in a large global sample. *Drug Alcohol Depend*. 2013;131(1–2):106–111.
23. Kay SR, Fiszbein A, Opler LA. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. *Schizophr Bull*. 1987;13(2):261–276.
24. Harel-Fisch Y. Trend of substance use among Israel youth: findings from the Israel-HBSC survey 1994–2011. Israel Anti-Drug Authority (IADA) Web site. http://www.antidrugs.gov.il/download/files/%D7%A1%D7%A7%D7%A8%20HBSC%202011%20%D7%A1%D7%95%D7%A4%D7%99%20%D7%9E%D7%99%D7%A2%D7%9C_2.pdf. 2013.
25. Konings M, Henquet C, Maharajh HD, et al. Early exposure to cannabis and risk for psychosis in young adolescents in Trinidad. *Acta Psychiatr Scand*. 2008;118(3):209–213.
26. Arseneault L, Cannon M, Poulton R, et al. Cannabis use in adolescence and risk for adult psychosis: longitudinal prospective study. *BMJ*. 2002;325(7374):1212–1213.
27. Stefanis NC, Delespaul P, Henquet C, et al. Early adolescent cannabis exposure and positive and negative dimensions of psychosis. *Addiction*. 2004;99(10):1333–1341.
28. Onaivi ES, Sugiura T, Di Marzo V. *Endocannabinoids: The Brain and Body's Marijuana and Beyond*. Boca Raton, FL: CRC Press; 2006.
29. Bac P, Pages N, Herrenknecht C, et al. Measurement of the three phases of muricidal behavior induced by delta9-tetrahydrocannabinol in isolated, fasting rats. *Physiol Behav*. 1998;63(5):815–820.
30. Bac P, Pages N, Herrenknecht C, et al. THC aggravates rat muricide behavior induced by two levels of magnesium deficiency. *Physiol Behav*. 2002;77(2–3):189–195.
31. Schubart CD, Sommer IEC, van Gastel WA, et al. Cannabis with high cannabidiol content is associated with fewer psychotic experiences. *Schizophr Res*. 2011;130(1–3):216–221.
32. Di Forti M, Morgan C, Dazzan P, et al. High-potency cannabis and the risk of psychosis. *Br J Psychiatry*. 2009;195(6):488–491.
33. Morgan CJA, Curran HV. Effects of cannabidiol on schizophrenia-like symptoms in people who use cannabis. *Br J Psychiatry*. 2008;192(4):306–307.
34. Zuardi AW, Crippa JAS, Hallak JEC, et al. Cannabidiol, a Cannabis sativa constituent, as an antipsychotic drug. *Braz J Med Biol Res*. 2006;39(4):421–429.
35. Moreira FA, Guimarães FS. Cannabidiol inhibits the hyperlocomotion induced by psychotomimetic drugs in mice. *Eur J Pharmacol*. 2005;512(2–3):199–205.
36. Leweke FM, Piomelli D, Pahlisch F, et al. Cannabidiol enhances anandamide signaling and alleviates psychotic symptoms of schizophrenia. *Transl Psychiatr*. 2012;2(3):e94.
37. Castaneto MS, Gorelick DA, Desrosiers NA, et al. Synthetic cannabinoids: epidemiology, pharmacodynamics, and clinical implications. *Drug Alcohol Depend*. 2014;144:12–41.