The Relevance of Sex in the Association of Synthetic Cannabinoid Use With Psychosis and Agitation in an Inpatient Population

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ABSTRACT

Background: Current evidence suggests that women are more sensitive to the effects of cannabinoids. The aim of this study was to investigate the relevance of sex in the association of synthetic cannabinoid (SC) use with psychosis and agitation.

Methods: A retrospective chart review was conducted for patients admitted to a psychiatric unit (2014–2016) to extract information on demographic factors, use of substances, clinical symptoms, and pharmacologic treatments. Study groups were defined as SC users (anyone who reported use of SCs over the past 3 months), cannabis users (positive toxicology screen for Δ^9-tetrahydrocannabinol [THC]), and controls (those who denied use of SCs over the past 3 months and had negative toxicology for THC).

Results: Digital charts of 983 patients were reviewed. A total of 162 subjects reported use of SCs over the past 3 months (76% male), and 292 subjects had positive toxicology screen for THC (67% male). A total of 38.9% of SC users (n = 63) had positive urine toxicology screen for THC. SC users had higher risks of psychotic presentations (adjusted odds ratio [AOR] = 3.390; 95% CI, 1.390–8.267) and agitation (AOR = 4.643; 95% CI, 1.974–10.918) compared to the controls. While women had lower rates of psychosis than men in the cannabis and control groups, the rates were markedly potentiated with SC use to high levels (79%) approximately equal to that seen in men (80%). There was also a significant interaction between SC use and sex for agitation (AOR = 0.308; 95% CI, 0.117–0.808). Female SC users were significantly more agitated than male SC users (73.7% vs 47.6%, respectively, $P = .005$).

Conclusions: SC users are more likely than nonusers to be psychotic or agitated in an inpatient setting. The potentiated rates of psychosis and agitation with SC use in women suggest that they may have a greater sensitivity to these synthetic compounds.

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Synthetic cannabinoids (SCs), which are commonly known as K2/Spice and have become popular as recreational drugs in the United States since 2009, mimic the effects of cannabis but are much more potent and efficacious at cannabinoid receptors. Whereas Δ^9-tetrahydrocannabinol (THC), the main psychoactive compound in cannabis, is a partial agonist of cannabinoid receptors, most of the SC compounds are full agonists, with higher potency and affinity to cannabinoid receptors.[1] Clinical studies are limited, but severe adverse effects of SCs on mental health have been reported in case series, emergency room reports, and psychiatric inpatients; the findings indicate that psychosis and agitation are the most frequent psychiatric presentations of SC use.[2–6]

Although SC use is more prevalent among men, and there is no report on the relevance of sex on the psychiatric presentation of SC use, accumulating evidence from animal and human studies suggests that females are more sensitive to some of the effects of cannabinoids. Animal studies report that female rodents are more sensitive to cannabinoid-induced locomotor suppression,[7] antinociception,[7–9] and hypothermia.[10] Females also acquire self-administration[11] and tolerance[9] of cannabinoids more rapidly. Although human studies are limited, current evidence suggests that women may be more vulnerable. As compared to men, women have shorter time periods between first cannabis use and problematic use, known as "telescoping"[12,13]; higher subjective effects of cannabis[14]; and worse cannabis withdrawal symptoms such as irritability, anger, and violent outbursts.[15–17] Regarding the relationship between use of cannabinoids and psychosis,[18,19] the typical later onset of psychotic symptoms in women compared to men[20] is significantly reduced among cannabis users.[21]

Because SCs are potent full agonists of cannabinoid receptors, the higher sensitivity of women to cannabinoids makes them more vulnerable to adverse effects of SCs. Previously, we conducted a retrospective chart review[22] investigating the psychiatric presentations of patients admitted to a dual diagnosis unit in 1 year (March 2014 to February 2015) with use of SCs and found that they presented more frequently with psychosis and agitation compared to cannabis users. However, the small sample number of female SC users prevented us from exploring sex differences. In the current study, we expanded our chart review across 3 years to investigate the potential contribution of sex in the association of use of SCs with

Clinical Points

- Compared to men, women have higher sensitivity to synthetic cannabinoids. Synthetic cannabinoids (commonly known as K2/Spice) are similar to cannabis but have higher potency and efficacy. No study has previously addressed potential differences in the clinical presentations of female versus male SC users.
- Women who report recent use of SCs more frequently presented with agitation and needed longer hospitalizations compared to men.

psychosis and agitation. Considering the high potency and efficacy of SCs on cannabinoid receptors and the higher sensitivity of women to the effects of cannabinoids in preclinical and clinical studies, we hypothesized that women would have more psychotic and agitated presentations associated with the use of SCs as compared to men.

METHODS

Study Design

A retrospective chart review was conducted with electronic records of all patients who were admitted to a dual diagnosis psychiatric unit at Mount Sinai Beth Israel (MSBI) from January 1, 2014, to December 31, 2016. MSBI is a university-affiliated hospital in downtown Manhattan, New York City. The MSBI dual diagnosis unit mostly serves patients with a history of substance use disorder comorbid with other psychiatric conditions. For this study, we included all patients with recent (past 3 months) use of cannabinoids, including natural (confirmed by urine toxicology) or synthetic (self-reported) cannabis. Additionally, we randomly selected a group of patients from the same unit, who denied recent use of cannabinoids and had negative toxicology for natural cannabis, as a non–cannabinoid using control group. Patients were excluded if urine toxicology screen results were not available. Patients were given a study ID number, and all extracted data were deidentified. Only the first admission information was included in the study if a patient was admitted to the unit more than once. This study was approved by the Icahn School of Medicine, MSBI Institutional Review Board.

Assessments

Digital charts of patients were reviewed and data for specified study variables were extracted. All available data were used, including admission history and physical examination results, progress notes, reports of administered medications, laboratory results, and discharge summaries. Psychotic symptoms were determined as present based on objective signs or clinical evaluations of both positive and negative symptoms (dichotomous variable). Presence of agitation was determined by whether or not a patient required *pro re nata* (administer when required) medication for episodes of severe agitation (dichotomous variable). Urine toxicology screening results identified current comorbid use of other substances (ie, cocaine, opioids, benzodiazepines, phencyclidine [PCP], and amphetamines). Blood alcohol level measurement identified alcohol intoxication. Prescribed antipsychotic medications were documented from discharge summaries and were converted to haloperidol-equivalent doses for both first-generation[23] and second-generation[24] antipsychotics. Length of hospital stay was calculated based on the number of days of inpatient hospitalization.

Data Analysis

We analyzed all data using IBM SPSS Statistics for Windows, version 23 (IBM; Armonk, New York). Study groups are identified as SC users (the SC group, which included SC+/marijuana [MJ]+ and SC+/MJ− patients), natural cannabis/marijuana users (the MJ group, which included MJ+/SC−), and control group (MJ−/SC−) groups. Data are presented using means, percentages, and 95% CIs. Univariate analyses were performed using analysis of variance, *t* test, and χ^2 to compare the variables between study groups. When any significant differences were determined, bivariate logistic regression analyses were performed to calculate adjusted odds ratios (AORs), with psychosis and agitation as dependent variables in 2 separate models and sex, age, and use of other drugs as covariates. Sex interaction with cannabinoid use was also included in both models. Similar regression analyses were performed to calculate AORs for the effects of sex on psychosis and agitation separately in each study group (SC, MJ, and non–cannabinoid using controls), with psychosis and agitation as dependent variables and age and use of other drugs as covariates.

RESULTS

Sociodemographic

Digital charts of 983 patients were reviewed. Full demographic results for study groups are shown in Table 1. A total of 162 subjects reported recent use of SCs and 292 subjects had recent use of cannabis. Among SC users, 38.9% (63 individuals) had positive urine toxicology screen for natural cannabis. SC and cannabis users were significantly younger than non–cannabinoid using controls (mean age = 34.88, 34.95, and 42.41 years, respectively). There were significantly more black individuals in the SC group (Table 1). When sociodemographic factors between men and women were compared, female cannabis users were significantly younger than male users (32.44 vs 36.15 years, respectively), and the group had more black individuals (55.6% vs 36.5%, respectively) (Table 1). There were no other significant sociodemographic differences between men and women.

Psychiatric Diagnosis and Use of Substances

Overall, 50.7% of our subjects (54.2% of men vs 42% of women) were diagnosed with a psychotic disorder, including schizophrenia (16.9% total, 20.0% of men vs 9.2% of women), schizoaffective disorder (18.0% total, 18.0% of men vs 10.0% of women), and unspecified psychotic disorder (15.8% total,

Table 1. Sociodemographic Factors for Synthetic Cannabinoid Users, Cannabis Users, and Controls

	Overall Comparison		Comparison by Sex		
Variable	Total	*P* Value	Men	Women	*P* Value
Size of study group (total n = 983), n (%)		…			
Synthetic cannabinoid	162 (16.5)		124 (76.5)	38 (23.5)	…
Cannabis	292 (29.7)		198 (67.8)	94 (32.2)	…
Control	529 (53.8)		377 (71.3)	152 (28.7)	…
Age, mean (SD), y (n = 983)		< .0001			
Synthetic cannabinoid	34.88 (10.58)		34.89 (10.23)	34.82 (11.79)	.968
Cannabis	34.95 (11.95)		36.15 (11.72)	32.44 (12.09)	.013
Control	42.41 (12.73)		42.70 (12.84)	36.15 (11.72)	.401
Ethnicity (total n = 954), n (%)[a]		< .001			
Synthetic cannabinoid					.635
White	27 (17.2)		20 (16.8)	7 (18.4)	
Black	95 (60.5)		71 (59.7)	24 (63.2)	
Hispanic	30 (19.1)		25 (21.0)	5 (13.2)	
Cannabis					.020
White	103 (36.5)		80 (41.7)	23 (25.6)	
Black	120 (42.6)		70 (36.5)	50 (55.6)	
Hispanic	52 (18.4)		37 (19.3)	15 (16.7)	
Control					.723
White	186 (36.1)		133 (36.3)	53 (25.6)	
Black	183 (35.5)		134 (36.6)	49 (32.9)	
Hispanic	135 (26.2)		91 (24.9)	44 (29.5)	
Single/divorced (total n = 983), n (%)		.423			
Synthetic cannabinoid	162 (100)		124 (100)	38 (100)	…
Cannabis	292 (100)		198 (100)	94 (100)	…
Control	527 (99.6)		376 (99.7)	151 (99.3)	.492
Unemployed (total n = 978)[b]		.002			
Synthetic cannabinoid	152 (94.4)		116 (94.3)	36 (94.7)	.641
Cannabis	240 (82.8)		164 (83.7)	76 (80.9)	.330
Control	463 (87.9)		327 (87.0)	136 (90.1)	.203

[a]A small number of subjects were of other races; these individuals were not included in these calculations.
[b]Data missing for some individuals.

Table 2. Psychosis, Haloperidol-Equivalent Dose of Antipsychotic Medications, Agitation, and Length of Hospital Stay in Synthetic Cannabinoid Users, Cannabis Users, and Controls

	Overall Comparison		Comparison by Sex		
Variable	Total	*P* Value	Men	Women	*P* Value
Psychotic presentations, n (%)		< .001			
Synthetic cannabinoid	129 (79.6)		99 (79.8)	30 (78.9)	1.000
Cannabis	168 (57.5)		121 (61.1)	47 (50.0)	.077
Control	235 (44.4)		175 (46.4)	60 (39.5)	.149
Haloperidol-equivalent dose of antipsychotic medications, mean (SD)		< .001			
Synthetic cannabinoid	10.72 (7.77)		10.25 (7.47)	11.96 (8.67)	.264
Cannabis	5.15 (6.87)		5.80 (7.13)	3.79 (6.11)	.019
Control	5.27 (7.08)		5.47 (7.25)	4.77 (6.65)	.305
Agitation,[a] n (%)		< .001			
Synthetic cannabinoid	87 (53.7)		59 (47.6)	28 (73.7)	.005
Cannabis	116 (39.7)		82 (41.4)	34 (36.2)	.443
Control	156 (29.5)		118 (31.3)	38 (25.0)	.171
Length of hospital stay, mean (SD), d		< .001			
Synthetic cannabinoid	15.19 (11.31)		14.23 (10.91)	18.43 (12.14)	.047
Cannabis	10.73 (8.56)		10.91 (9.27)	10.35 (6.85)	.604
Control	12.40 (12.11)		12.67 (12.83)	11.70 (10.13)	.405

[a]Presence of agitation was indicated by as-needed medication administration.

16.2% of men vs 14.8% of women). Other main diagnoses were unspecified depressive disorder (37.3% total, 34.6% of men vs 44.0% of women) and bipolar disorder (8.1% total, 7.6% of men vs 9.5% of women). Regarding comorbid use of substances, cannabis was the most common drug (36.1% total, 35.3% of men vs 38.0% of women), followed by cocaine (21.7% total, 19.9% of men vs 26.1% of women), opioids (17.6% total, 17.7% of men vs 17.3% of women), and self-reported use of SCs (16.6% total, 17.8% of men vs 13.4% of women). There were no significant differences between men and women in use of any substances except for cocaine, which was more common in women ($P = .021$).

Psychosis and Agitation

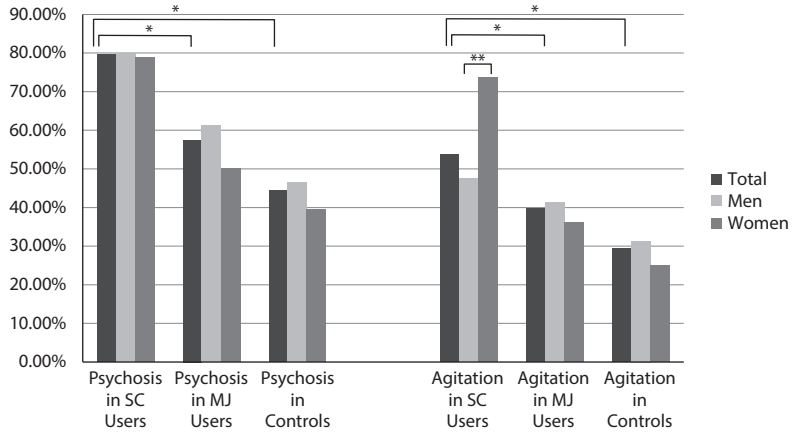
Psychotic presentations were significantly more frequent in SC users (79.6%) compared to cannabis users (57.5%)

Table 3. Adjusted Odds Ratios (AORs) for Psychosis and Agitation in Synthetic Cannabinoid Users and Cannabis Users Compared to Non–Cannabinoid Using Controls[a]

	Psychotic Symptoms			Agitation		
Variable	AOR	95% CI	*P* Value	AOR	95% CI	*P* Value
Non–cannabinoid using controls (reference)	…		< .001	…		.001
Cannabis users	1.022	0.571–1.828	.943	0.904	0.490–1.668	.748
Synthetic cannabinoid users	3.390	1.390–8.267	.007	4.643	1.974–10.918	< .001
Age	0.987	0.975–1.000	.044	0.978	0.966–0.990	< .001
Sex	1.347	0.867–2.092	.186	1.144	0.762–1.819	.569
Alcohol use	0.256	0.161–0.406	< .001	0.381	0.232–0.627	< .001
Cocaine use	0.679	0.474–0.972	.035	0.514	0.348–0.760	.001
Opioid use	0.396	0.256–0.613	< .001	0.615	0.385–0.984	.043
Benzodiazepines use	0.413	0.253–0.676	< .001	0.748	0.448–1.247	.265
Amphetamine use	1.161	0.603–2.235	.656	0.703	0.355–1.396	.314
Phencyclidine use	0.813	0.295–2.240	.688	0.303	0.085–1.086	.067
Cannabinoid use × sex	…		.319	…		.015
Cannabis use × sex	1.634	0.814–3.281	.168	1.362	0.663–2.794	.400
Synthetic cannabinoid use × sex	0.888	0.316–2.494	.821	0.308	0.117–0.808	.017

[a]Odds ratios were adjusted for age, sex, and use of other drugs.

Figure 1. Agitation and Psychosis in the Total Sample, Men, and Women



*P < .001.
**P < .005.
Abbreviations: MJ = natural cannabis/marijuana, SC = synthetic cannabinoid.

and the non–cannabinoid using control group (44.4%) (P < .001). Moreover, SC users were prescribed higher doses of antipsychotic medications based on the haloperidol-equivalent doses of prescribed antipsychotic medications (mean = 10.72 mg) compared to cannabis users (mean = 5.15 mg) and the non-–cannabinoid using control group (mean = 5.27 mg) (P < .001). Agitation had the same pattern, with higher presentation in SC users (53.7%) compared to cannabis users (39.7%) and the non–cannabinoid using control group (29.5%) (P < .001). Length of hospital stay was also significantly longer in SC users (15.19 days), but shorter in cannabis users (10.73 days) compared to controls (12.40 days) (P < .001) (Table 2). Table 3 provides the AORs for the presence of psychotic symptoms and agitation in the whole sample. The data show that the SC users had a significantly higher risk of psychotic presentations (AOR = 3.390, P = .007) and agitation (AOR = 4.643, P < .001) compared to the non–cannabinoid using control group. There was a significant interaction of SC use and sex with agitation (P = .017).

To examine the association between use of cannabinoids with psychosis and agitation in those individuals who used both SC and cannabis compared to those who only used only SC (negative urine toxicology screen), a post hoc analysis was conducted with the subjects regrouped into 4 groups: only SC (SC+/MJ–), only cannabis (SC–/MJ+), both SC and cannabis (SC+/MJ+), and no cannabinoids (SC–/MJ–). The results demonstrated that the SC+/MJ– group more frequently presented with psychosis (84.8%), followed by the SC+/MJ+ group (71.4%), the SC–/MJ+ group (57.5%), and the SC–/MJ– group (44.4%) (P < .001). Similarly, the SC+/MJ– group required the highest dose of antipsychotic medications based on the haloperidol-equivalent dose (mean [SD] = 11.59 [9.94] mg), followed by the SC+/MJ+ (9.37 [7.37] mg), SC–/MJ+ (5.20 [6.87] mg), and SC–/MJ– (5.27 [7.08] mg) groups (P < .001). Agitation was equally high in the SC+/MJ+ (54%) and SC+/MJ– (53.5%) groups, with lower rates in other 2 groups (39.7% in the SC–/MJ+ group and 29.5% in the SC–/MJ– group) (P < .001). The longest hospital stay was observed in the SC+/MJ– group (mean [SD] = 16.61 [12.36] days), followed by SC+/MJ+ (12.92 [9.01] days) and SC–/MJ– (12.39 [12.11] days), and the shortest hospital stay was for the SC–/MJ+ group (10.73 [8.56] days) (P value < .001).

Sex Differences in Psychosis

The presence of psychotic symptoms and the dose of prescribed antipsychotic medications were compared between men and women in each study group (Figure 1). Among cannabis users, there was a trend of less frequent psychotic presentations in women (50.0%) compared to men (61.1%) (P = .077) (Table 2). After control for demographic factors and use of other drugs, this difference became significant (AOR = 0.48 P = .009) (Table 4). In

Table 4. Adjusted Odds Ratios (AORs) for Psychosis and Agitation in Female Compared to Male Synthetic Cannabinoid Users, Cannabis Users, and Non–Cannabinoid Using Controls[a]

	Psychotic Symptoms			Agitation		
Variable	AOR	95% CI	*P* Value	AOR	95% CI	*P* Value
Synthetic cannabinoid users						
Female (male as reference)	0.721	0.268–1.940	.517	3.202	1.271–9.070	.014
Age	0.974	0.936–1.014	.206	0.968	0.935–1.003	.074
Alcohol use	1.134	0.127–10.118	.910	0.282	0.051–1.544	.144
Cocaine use	1.274	0.369–4.401	.701	0.428	0.146–1.255	.122
Opioid use	0.131	0.027–0.623	.011	0.137	0.015–1.235	.076
Benzodiazepine use	0.707	0.134–3.731	.683	1.350	0.247–7.397	.729
Amphetamine use	1.677	0.104–27.110	.716	0.0	0.0	—
Phencyclidine use	0.087	0.007–1.037	.053	0.0	0.0	—
Cannabis users						
Female (male as reference)	0.480	0.277–0.833	.009	0.684	0.393–1.190	.179
Age	0.989	0.967–1.011	.316	0.977	0.955–0.999	.038
Alcohol use	0.347	0.157–0.764	.009	1.118	0.514–2.431	.778
Cocaine use	0.604	0.322–1.132	.116	0.522	0.264–1.034	.062
Opioid use	0.470	0.217–1.020	.056	0.795	0.355–1.780	.577
Benzodiazepine use	0.423	0.14–0.925	.031	0.923	0.420–2.027	.841
Amphetamine use	0.813	0.285–2.323	.700	1.081	0.386–3.028	.882
Phencyclidine use	0.811	0.150–4.396	.808	0.958	0.166–5.522	.962
Controls						
Female (male as reference)	0.737	0.471–1.154	.182	0.874	0.543–1.406	.579
Age	0.988	0.972–1.004	.133	0.980	0.963–0.996	.018
Alcohol use	0.174	0.090–0.335	<.001	0.184	0.084–0.402	<.001
Cocaine use	0.639	0.395–1.034	.068	0.517	0.302–0.885	.016
Opioid use	0.393	0.221–0.699	.001	0.607	0.320–1.149	.125
Benzodiazepine use	0.371	0.181–0.761	.007	0.518	0.231–1.159	.110
Amphetamine use	1.489	0.621–3.575	.372	0.265	0.076–0.923	.037
Phencyclidine use	1.616	0.412–6.337	.491	0.235	0.028–1.983	.183

[a]Odds ratios were adjusted for age and use of other drugs.

contrast, in SC users, the rate of psychosis in women was high, achieving levels similar to those of men (79.8% of men vs 78.9% of women, $P = 1.000$) (Table 2). There were no significant differences in the dose of prescribed antipsychotic medications (based on calculated haloperidol-equivalent dose) between men and women among SC users (10.25 mg in men vs 11.96 mg in women, $P = .264$) and non–cannabinoid using controls (5.47 mg in men vs 4.77 mg in women, $P = .305$), but among cannabis users, women were prescribed lower doses of antipsychotic medications (5.80 mg in men vs 3.79 mg in women, $P = .019$) (Table 2).

Sex Differences in Agitation in Study Groups

There were no significant differences in the presence of severe agitation episodes between men and women in the non–cannabinoid using control group (31.1% in men vs 25% in women, $P = .171$) or cannabis users (41.4% of men vs 36.2% of women, $P = .443$), but female SC users were significantly more likely to be agitated compared to male SC users (47.6% of men vs 73.7% of women, $P = .005$) (Table 2). The higher risk of agitation in female SC users remained significant after adjustment for age and use of other drugs (AOR = 3.202, $P = .014$) (Table 4).

Sex Differences in Length of Hospital Stay

There were no significant differences in length of hospitalization between men and women in the non–cannabinoid using group and cannabis users, but in SC users, women had significantly longer hospitalizations compared to men (14.23 days for men vs 18.43 days for women, $P = .047$) (Table 2).

DISCUSSION

The results of this study confirmed and extended our previous findings that SC users are more likely than nonusers to have psychotic symptoms and agitation presentations.[22] SC users were 3 times more likely to be psychotic and over 4 times more likely to have agitation compared to the control group. They also received higher doses of antipsychotic medications and had longer hospital stays. These findings are consistent with the literature reporting severe symptoms of psychosis and agitation as the main psychiatric presentations of SC use.[2–6,25] Our study now also demonstrates significant sex differences in the association of use of cannabinoids with psychosis and agitation. While women tended to have fewer psychotic presentations among non–cannabinoid using controls (trend-level) and cannabis users (significant) compared to men, there were equivalently high rates of psychosis in men and women among SC users. Moreover, the risk of agitation was markedly higher in women compared to men among SC users. To the best of our knowledge, this report is the first to document sex differences in the clinical presentations of SC use.

SC compounds are potent full agonists of cannabinoid receptors[26] and lack cannabidiol (CBD), which has been shown to have antipsychotic properties in clinical trials.[27,28] Our finding that SC users had a higher rate of psychotic

symptoms compared to cannabis users fits in line with the accumulating evidence of a dose-response/cannabinoid receptor type 1 [CB_1] potency relationship between the use of cannabinoids and psychosis[29] and higher rates of psychosis within high-potency (higher ratio of THC to CBD) cannabis users.[30]

There is limited clinical information about sex in relation to the use of cannabinoids and psychosis, except that the typically later onset of psychosis in women[20] is diminished in cannabis users.[21,31] Our results demonstrated that women with cannabis use present less frequently with psychosis compared to men in a psychiatric dual-diagnosis inpatient setting. It is important to note that we have no data on the amount of cannabis used by our subjects due to the nature of retrospective chart reviews. Some studies have reported that, whereas there are no sex differences in the amount or frequency of cannabis use between male and female cannabis users in healthy individuals, among psychotic patients, men use cannabis more frequently and in larger amounts compared to women.[32] Possible heavier cannabis use in male psychotic patients may explain the higher rate of psychotic presentations in male cannabis users in our inpatient sample. There were, however, no available data available on the amount and frequency of SC use in the patients.

The fact that SC use in women induced marked psychosis to the high levels seen in men might indicate a potential greater sensitivity of women to full agonist cannabinoids. Controlled human laboratory experiments are not possible to conduct with SC agents considering their health risk, so evaluating aspects of metabolism and pharmacokinetics or the psychogenic effects of SCs in women versus men is difficult to do. Animal studies have, however, demonstrated that female rats acquire self-administration of synthetic cannabinoid (WIN55,212-2) to a faster extent than males[11] and administer a greater amount of the drug.[33]

Our finding that patients with SC use, particularly women, have significantly more frequent presentations of agitation is of significant interest and has potential clinical importance. A possible bias toward prescribing lower doses of medications to women could be a possible explanation for the occurrence of more agitation episodes in female SC users, but our data show there is no difference in the dose of prescribed antipsychotic medications between male and female SC users. The effect of cannabinoids on agitation and aggression has been studied extensively in animal models for many decades. While some studies report that cannabis exposure decreases aggression in different animal species,[34–37] other studies report an increase in aggressive behaviors[38–40] with a dose-response relationship.[41] Theories to reconcile these conflicting results suggest that cannabis suppresses innate (predatory and intermale) aggression but increases irritable aggression and agitation in stressful situations (reviewed by Abel[42]), which has been consistently demonstrated in several studies[43–47] and is shown to be magnified by estrogen in females.[48]

Similar to animal models, human studies report both decreases[49] and increases in aggressive behaviors in cannabis users.[50] While cannabis may have calming effects in the general population,[49] increases in aggression and agitation are observed in individuals with psychiatric vulnerability,[25,51] such as those within inpatient units[52,53] and those with first-episode psychosis.[54] Similar to findings in animal models, different doses and levels of acute or chronic stress may explain these different effects in humans. In our study, cannabis use had no association with agitation. Unfortunately, our study design did not allow us to ascertain the dose of cannabis used or stress levels experienced by patients. However, SC users in our study did demonstrate significantly more agitation, which was significantly greater in women compared to men. Given the enhanced pharmacologic potency of SCs, our findings may support a dose-response/CB_1 potency relationship between greater cannabinoid receptor agonists (SC vs THC) and agitation, particularly in women. More studies are needed to evaluate potential sex differences in relation to different doses and types of cannabinoids (eg, partial or full cannabinoid receptor agonists, light or heavy users) on agitation and aggression and in regard to the role of stress in this association. However, our findings suggest that female SC users may need an earlier start and higher dose of pharmacologic treatments in the course of their inpatient hospitalization compared to male SC users.

Limitations

Results from retrospective chart reviews have limitations that should be considered in interpreting the findings. First, there was no standardized measure for the patients' clinical signs and symptoms; thus, we could not systematically address the severity of psychosis or agitation. However, raters used all available data to evaluate patients' presentations and were not limited to any one specific clinical document, such as admission or discharge summaries. Moreover, to standardize our measure of agitation, we used the administration of as-needed medications given for episodes of severe agitation, which is documented precisely in patients' charts. Second, another challenge is that standardized clinical urine toxicology reports do not test for SCs, so data on SC use were based solely on patients' self-report on their use over the past 3 months. In fact, these compounds vary in potency and chemical structure, making them difficult to detect even using sophisticated analytic assays. It is possible that some patients chose to withhold information about drug use from their physicians, which may cause selection bias. Nevertheless, even if patients underreported their SC use, the data still showed significant differences between those with and without a positive self-report of SC. Moreover, since the exact date of last SC use within the past 3 months was not available in the charts, it is not possible to differentiate acute effects of SCs from more persistent effects that may last for weeks. In addition, we did not have detailed information on the frequency and amount of use of substances, including SCs and natural cannabis, which is particularly important considering the well-known dose-response relationship between use of cannabis and psychosis.[29] Future studies that include a prospective study design with more detailed information obtained regarding patients' substance use,

including laboratory-verified SC consumption, will enhance interpretation of the data. Finally, our patient cohort was selected from an inpatient psychiatric unit and as such could have presented with more severe symptoms and other comorbid psychopathologies that may have influenced their hospitalization outcome. Since this population was mostly unemployed and homeless and had histories of prior psychiatric admissions, caution should be taken in generalizing the current results to other SC users in non-psychiatric populations. Overall, despite these and other limitations, our general observations are consistent with those of other reports which suggest that SC use is associated with increased risk of psychosis and agitation, and the initial findings regarding sex differences may set the foundation for future studies.

CONCLUSION

Our study confirms that the use of synthetic cannabinoids is associated with higher presentation of psychosis and agitation in an inpatient population and that SC users were prescribed higher doses of antipsychotic medications and had longer hospital stays. There are significant sex differences in the association between cannabinoid use with psychosis and agitation, with female SC users more frequently presenting with agitation and having longer hospital admissions, and having similar high rates of psychosis, compared to male SC users. These findings emphasize the importance of considering sex when making decisions about the diagnosis and treatment of cannabinoid users in psychiatric impatient units.

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