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Psychiatric comorbidity associated with synthetic cannabinoid use compared to cannabis

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Abstract

Background: Synthetic cannabinoids (SC) use has had a dramatic increase in recent years, but data regarding their adverse effects on mental health is limited. In this study, we compared clinical presentations of SC users with cannabis users in a psychiatric inpatient setting.

Methods: Digital charts of all patients who were admitted to a dual diagnosis psychiatric unit in one year were reviewed. Patients who had any current substance use disorder were categorized in four groups: (1) SC use and cannabis use (SC+MJ+), (2) SC use without cannabis use (SC+MJ-), (3) cannabis use without SC use (SC-MJ+), and (4) No SC or cannabis use (SC-MJ-).

Results: A total of 594 charts were included. SC+MJ- patients had significantly more psychotic symptoms (OR: 4.44, 95% CI: 1.98–9.94), followed by SC+MJ+ (OR: 3.61, 95% CI: 1.87–6.97) and SC-MJ+ (OR: 1.87, 95%CI: 1.33–2.64) patients. The SC+MJ- group also had more agitation and aggression was most prominent in SC+MJ+ subjects. Multivariate analyses showed that the psychiatric associations of SC and cannabis use remained significant even after controlling for potential confounds such as other substance use.

Conclusions: The prominent psychiatric features of SC users as compared to cannabis users in an inpatient setting are psychotic presentations and agitation, which have important treatment implications.

Keywords

Synthetic cannabinoids, K2, Spice, cannabis, psychosis, agitation

Introduction

Synthetic cannabinoids (SCs), widely sold in the United States under brand names such as "K2" and "Spice", are generally cheap, easily available online or in "head shops" and "convenience stores", and are not detectable in standard drug screens (Seely et al., 2012). The dramatic increase in their use in recent years (Castaneto et al., 2014; Celofiga et al., 2014; Fantegrossi et al., 2014) and their reported serious adverse effects on mental health has now made them a key focus of public health concern. Calls to Poison Control Centers which increased from 14 in 2009 to 6968 in 2011, and thereafter declined in subsequent years, trended up again in 2014 and reached 3677 calls from 2665 in 2013 (Brewer and Collins, 2014; Wood, 2013). Recent data shows that Poison Control Centers received 3572 calls related to SC use in January–May 2015, which reflected a 229% increase from calls made during the same period in 2014 (Mowry et al., 2014). More than 11,000 ER visits related to SC use were reported in 2010 (Van Amsterdam et al., 2015), increasing to 28,531 in 2012 (Castaneto et al., 2014). Alarmingly, though SC use had a significant drop in 2015 in US high school seniors, it has been ranked as the second most common illicit substance used after cannabis since 2012 (Johnston et al., 2016), and a recent cohort study reported 17% lifetime prevalence of SC use in college students (Egan et al., 2015).

SCs are a heterogeneous group of compounds initially developed for research purposes in attempts to interrogate the endogenous cannabinoid receptor in relation to its interactions with diverse cannabimimetic ligands. The recreational use of these drugs started in 2005 in Europe and 2009 in the United States. So far more than 300 SC compounds have been synthesized, and with the rapid emergence of their new compositions, it is difficult to know their effects on physical and mental health (Fantegrossi et al., 2014). An increasing number of case reports from emergency rooms indicate a pronounced intoxication and serious adverse effects of SC use (van Amsterdam et al., 2015), which appear to be more serious than from cannabis use (Glue et al., 2013). The most common neuropsychiatric symptoms among them are acute psychosis, agitation, irritability and anxiety (Hermanns-Clausen et al., 2013; Kamijo et al., 2014; Papanti et al., 2013).

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The relationship between psychosis and natural cannabis use is well-known in epidemiological studies, with a roughly twofold increase of psychosis in cannabis users (Burns, 2013; Gage et al., 2016). An increased risk of psychosis of about 40% was reported in a recent meta-analysis in individuals who had ever used cannabis, with an even larger effect up to 200% for heavy users (Moore et al., 2007). Cannabis contains more than 80 cannabinoids, and it is believed that THC is the main psychoactive component which is responsible for the association between increased psychosis and cannabis use (Iseger and Bossong, 2015). In laboratory settings THC is reported to induce brief psychotic-like presentations in healthy volunteers (Morrison et al., 2009). Other components of the cannabis plant such as cannabidiol (CBD) exhibit antipsychotic and anxiolytic properties in preclinical studies (Iseger and Bossong, 2015). While THC binds to cannabinoid receptor types 1 and 2, CBD has little binding affinity to these receptors (McPartland et al., 2015). Over the last decade, several studies have reported that cannabis strains with a higher ratio of THC to CBD have a stronger association with psychosis (Van Amsterdam et al., 2015). A recent study underscored the increased risk of psychotic disorders in users of high potency cannabis (skunk) with high THC/CBD ratio as compared to low potency cannabis (hash) (Di Forti et al., 2015).

SC compounds, similar to high potency cannabis, lack CBD. Furthermore, while THC is a partial agonist for cannabinoids receptors, most SCs are full agonists (Brewer and Collins, 2014; Celofiga et al., 2014;), with a 4–5 times higher affinity (Elsohly et al., 2014) and a 40–660 times higher functional potency compared to cannabis (van Amsterdam et al., 2015). These factors suggest that SC compounds may have stronger association with psychosis in comparison to natural cannabis, and recent clinical reports as well as data from emergency room settings have provided evidence in support of that relationship (Hurst et al., 2011).

Though there is increasing evidence of severe negative effects of SCs on mental health, and particularly psychosis and agitation, it is largely limited to case reports and brief observations in emergency rooms. In a systematic review in 2014, only five reports from psychiatric inpatient units were found, summarizing a total of 33 patients with psychotic presentations (Castaneto et al., 2014). Moreover, most of the reported patients used other substances, particularly cannabis, in addition to SCs (Winstock and Barratt, 2013) and there is a lack of knowledge about the association of SC use with psychosis in comparison to cannabis.

In this study, we evaluated clinical presentations between SC users and cannabis users who needed psychiatric inpatient treatment to determine the specific protracted psychiatric effects of SC in comparison to cannabis users. We also investigated the unique association of SC use with psychosis, controlling for basic demographic factors and use of other substances. We hypothesized that SC use has a stronger association with psychosis compared to cannabis, and that this association is independent of use of other substances.

Methods

Study design

This study is a retrospective chart review. Digital charts of all patients who were admitted to a Dual Diagnosis psychiatric unit at Mount Sinai Beth Israel (MSBI) from March 1, 2014 to February 28, 2015 were reviewed. MSBI is a university-affiliated hospital in downtown Manhattan, New York. Patients get admitted to three psychiatric inpatient units after initial screening in the emergency room by a psychiatrist. The Dual Diagnosis unit mostly, but not exclusively, serves the patients with a history of substance use disorder. For this study, patients who denied any recent use of substances (last three months) and their urine toxicology was negative for all substances were excluded. All remaining patients who either reported substance use over the last three months or had a positive urine toxicology or alcohol level were categorized in four study groups based on their cannabis and SC use: (1) reported SC use and reported cannabis use or urine toxicology positive for cannabis (SC+MJ+), (2) no reported SC use, but reported cannabis use or urine toxicology positive for cannabis (SC-MJ+), (3) reported SC use, but denied cannabis use and had a negative urine toxicology for cannabis (SC+MJ-), and (4) no report of SC or cannabis use, and urine toxicology negative for cannabis (SC-MJ-). Patients were given a study code, and all extracted data was de-identified. This study was approved by the Mount Sinai Beth Israel Institution Review Board.

Assessments

Digital charts of all patients were reviewed and data was extracted for the study variables (Table 1). All available data were used, including admission history, progress notes of all treatment team members, reports of administrated medications, laboratory results, and discharge summaries. Diagnosis was made by patients' treating psychiatrists based on DSM-V criteria and was collected from discharge summaries. Clinical symptoms were extracted from admission notes, progress notes, mental status reports, and discharge summaries. Symptoms were categorized to five groups: (1) psychosis, (2) mood symptoms, (3) suicidality, (4) agitation, and (5) aggression. Symptoms were considered as present if they were documented in the charts at any time over the course of patients' hospitalization, based on objective signs or clinical evaluations and not just based on patients' self-reports. Aggression included both verbal and physical aggressive behaviors, both on the day of admission outside the hospital based on documented reports (mainly reason for admission) and observed behaviors over the course of hospitalization. Substance use history was self-reported use of any drugs in the last three months, urine toxicology, and alcohol level on admission. Prescribed medications at discharge and administered *pro re nata* (PRN; administer when required) medications for aggression or agitation were collected. Doses of antipsychotic medications were converted to equivalent dose of Haldol (Andreasen et al., 2010).

Data analysis

We analyzed all data using SPSS 19. The data is presented using mean, percentage, and 95% confidence interval (CI). Univariate analyses were performed using analysis of variance (ANOVA) (Tukey post hoc) and chi-square, when appropriate, to compare the variables between four study groups. When any significant differences were determined between study groups, odds ratios were calculated for each group. Furthermore, to compare SC and cannabis groups specifically, based on a priori hypotheses, the

Table 1. List of variables and their definitions for the study.

Demographic	**Age**	Years
	Gender	Male, female
	Ethnicity	Caucasian, African American, Hispanic, Asian, Other
	Job	Employed, unemployed, student
	Residence	Private (with or without family), psychiatric residence, dormitory, shelter, or homeless
	Education	Some high school, finished High School/ GED, some college, college graduated and above
	Marital status	Married, single/divorced/separated
Symptoms	**Psychosis**	Thought disorganization, internally preoccupation, responding to internal stimuli
	Mood	Depressed, anxious or elated affect, social isolation, increased or decreased activity
	Suicidality	Suicide ideation: self-report active suicidal ideation Suicide attempt: suicide attempts before admission
	Agitation	Observed and documented agitation in the hospital
	Aggression	Documented evidence of verbal or physical aggressive behaviors on the day of admission or over the hospital course
Substance use	**Self-report**	Use of any drug use over last three months
	Urine toxicology	
	Alcohol level	
Medications	**PRN medications**	Number of incidents that a patient needed *pro re nata* medications for severe agitation or aggression in the inpatient unit (not including the medications at ER)
	Discharge medications	Antipsychotic, mood stabilizers, antidepressants and any other psychotropic medications at discharge
Diagnosis	**Discharge diagnosis**	Axis I diagnosis based on DSM-V criteria at discharge other than substance use disorders
Length of stay		Days of stay in inpatient unit (not including the time spent at ER)

MJ+SC- group and MJ-SC+ group were compared using t-test and chi-square for all study variables. Multivariate analyses were performed to investigate association between SC use as the independent variable and each of the following factors as the dependent variables in four different models: (1) symptoms of psychosis, (2) diagnosis of any psychotic disorders, (3) agitation, and (4) aggression (including both verbal and/or physical aggressive behaviors). In all logistic regression analyses, covariates were basic demographic factors (age, gender, and ethnicity), and use of all other drugs including cannabis. Each substance use was considered positive if the patient reported its use over last three months, or their laboratory results were positive. Non-overlapping CIs of the odds ratio was used to determine significantly-different associations among variables in the regression model.

Inter-rater reliability

All data were extracted from digital charts by two raters. We evaluated the inter-rater reliability by calculating Kappa coefficient for 30 charts selected randomly and rated by both raters. Kappa was 0.926 for psychosis, 0.837 for mood symptoms, 0.920 for suicidal ideation, 0.839 for agitation, and 0.914 for aggression.

Results

Study groups

A total of 676 patients were admitted to Mount Sinai Beth Israel Dual Diagnosis unit from March 1, 2014 to February 28, 2015. Electronic charts for all these patients were reviewed. 82 patients were excluded from the study as they denied any recent use of substances and their urine toxicology and blood alcohol level were negative. Data extracted from total of 594 charts was analyzed (Table 2). Overall, 47 (7.9%) patients had recent use of both cannabis and SC (SC+MJ+), 209 (35.2%) had recent use of cannabis with no SC use (SC-MJ+), 35 (5.9%) had recent SC use with no cannabis (SC+MJ-) and 303 (51.0%) of patients did not use cannabis or SC in the last three months (SC-MJ-) (Table 3).

Table 4 summarizes substance use data in the four study groups. Lifetime and current use of other substances were significantly different in the study groups for alcohol, cocaine, opiates, benzodiazepines, and ecstasy (Table 4).

Socio-demographic factors

The mean age of patients was 40.56 (SD: 12.88) and most were male (74.7%). African American patients were 38.0% of the population, follow by Caucasians (33.8%) and Hispanic (27.5%). Most patients were single/divorced/or separated (92.3%) and unemployed (86.5%). 59.2% had below college education and 43.0% were homeless (Table 2).

Comparing study groups, the mean age was significantly different between groups (p-<0.000). Post hoc analysis showed that the MJ-SC- group had significantly higher mean age (45.93, 95% CI: 44.61–47.24) compared to other groups, but age was not significantly different between other groups. Ethnicity was also significantly different between study groups (p<0.000). A greater number of African Americans were present in the $SC^{+}MJ^{-}$ and $SC^{+}MJ^{+}$ groups compared to SC-MJ- (p<0.001 for both), but there were no differences between SC-MJ+ and SC-MJ- groups. Gender, marital status, education, residential condition, and working situation were not significantly different between study groups.

Table 2. Demographic, clinical presentations, diagnoses, and medication management of all patients in the Dual Diagnosis unit.

N		594
Age mean (SD) (*n*=594)		40.56 (12.88)
Male (%) (*n*=594)		444 (74.7%)
Ethnicity (*n*=586)	**Caucasian**	198 (33.8%)
	African American	223 (38.0%)
	Hispanic	161 (27.5%)
	Asian	4 (.7%)
Unemployed (*n*=594)		514 (86.5%)
Single (*n*=594)		548 (92.3%)
Residence (*n*=591)	**Homeless**	254 (43.0%)
	Psychiatric residence	82 (13.9%)
	Apartment	255 (43.1%)
Education (*n*=274)	**Some high school**	74 (27.1%)
	Finished High School/GED	88 (32.1%)
	Some college	63 (23.0%)
	College graduated and above	49 (17.8%)
Presentation (*n*=594)	**Psychotic symptoms**	269 (45.3%)
	Mood symptoms	273 (46.0%)
	Suicide ideation	326 (54.9%)
	Suicide attempt	50 (8.4%)
	Agitation	151 (25.4%)
	Aggression	140 (23.6%)
Number of episodes that PRN medications were needed for agitation or aggression, mean (SD) (*n*=594)		1.1 (2.8)
Diagnosis (*n*=594)	**Schizophrenia**	92 (15.5%)
	Schizoaffective	95 (16.0%)
	Bipolar	47 (7.9%)
	MDD	10 (1.7%)
	Unspecified psychotic disorder	77 (13.0%)
	Unspecified depressive disorder	252 (42.4%)
	Others	21 (3.5%)
First episode		40 (6.7%)
Medications (*n*=594)	**No meds**	179 (30.1%)
	Antipsychotics	121 (20.4%)
	Mood stabilizer/antidepressants	101 (17.0%)
	Antipsychotic + mood stabilizer/antidepressants	168 (28.3%)
	Others	24 (4.0%)
Antipsychotic equivalent dose of Haldol (*N*: 280) (*n*=594)		11.57 (6.87)
Length of stay mean (SD) (*n*=594)		12.48 (12.31)

Psychotic presentations and medication management

Among all patients, 269 (45.3%) had objective signs of psychosis, and 263 (44.3%) were discharged with diagnosis of a psychotic disorder, such as schizophrenia, schizoaffective, or unspecified psychotic disorder. Of note only 40 (6.7%) patients were first episode in their psychiatric disorder; the majority of patients had previous episodes. With regard to medication management, overall, 289 (48.7%) patients were discharged on antipsychotic medications with or without other medications, with 11.57mg/day (SD: 6.87) equivalent dose of Haldol (Table 2).

Psychotic presentations had different frequencies among the study groups (p<0.000). SC+MJ- subjects were significantly associated with more psychotic symptoms (OR: 4.44, 95% CI: 1.98–9.94), followed by SC+MJ+ (OR: 3.61, 95% CI: 1.87–6.97) and SC-MJ+ (OR: 1.87, 95%CI: 1.33–2.64) individuals.

Diagnosis of psychotic disorders was also significantly different among the groups (p<0.000). SC+MJ- subjects were significantly associated with more psychotic disorder diagnoses (OR: 6.74, 95% CI: 2.75–16.50), followed by SC+MJ+ (OR: 4.78, 95% CI: 2.39–9.58) and SC-MJ+ (OR: 1.39, 95%CI: 1.01–1.96).

Furthermore, medication management differed significantly between study groups (p<0.000). SC+MJ- subjects were prescribed more antipsychotic medications (OR: 8.323, 95% CI: 2.898– 23.905), followed by the SC+MJ+ group (OR: 4.104, 95%CI: 2.003–8.410) and SC-MJ-, who had the least antipsychotic medication prescriptions (OR: 0.363, 95%CI: 0.259–0.510). Comparing the antipsychotic equivalent dose of Haldol, SC+MJ+ and SC+MJ- groups had no significant difference, but

Table 3. Demographic, clinical presentations, and medication management comparison between $SC^{+}MJ^{+}$, $SC^{-}MJ^{+}$, $SC^{+}MJ^{-}$, and $SC^{-}MJ^{-}$ groups.

		$SC^{+}MJ^{+}$	$SC^{+}MJ^{-}$	$SC^{-}MJ^{+}$	$SC^{-}MJ^{-}$	*P*-value
***N* (%)**		47 (7.9%)	35 (5.9%)	209 (35.2%)	303 (51.0%)	
Age mean (SD)		34.08 (11.02)	35.25 (11.75)	35.25 (11.92)	45.85 (11.69)	0.000
Male (%)		41 (87.2%)	25 (71.4%)	157 (75.1%)	221 (72.9%)	0.201
Ethnicity	**Caucasian**	6 (12.8%)	1 (2.9%)	71 (34.0%)	120 (39.6%)	0.000
	African American	28 (59.6%)	23 (65.7%)	78 (37.3%)	94 (31.0%)	
	Hispanic	13 (27.7%)	10 (28.6%)	56 (26.8%)	82 (27.1%)	
	Asian	0 (0%)	1 (2.9%)	1 (.5%)	2 (.7%)	
Unemployed		44 (93.6%)	32 (91.4%)	175 (83.7%)	263 (86.8%)	0.190
Single		46 (97.9%)	34 (97.1%)	195 (93.3%)	273 (90.1%)	0.136
Residence	**Homeless**	24 (51.1%)	15 (42.9%)	82 (39.2%)	133 (43.9%)	0.538
	Psychiatric residence	8 (17.0%)	8 (22.9%)	26 (12.4%)	40 (13.2%)	
	Apartment	15 (31.9%)	12 (34.3%)	100 (47.8%)	128 (42.2%)	
Education	**Some High School**	12 (25.5%)	6 (17.1%)	26 (12.4%)	30 (9.9%)	0.103
	Finished High School/ GED	2 (4.3%)	7 (20.0%)	27 (12.9%)	52 (17.2%)	
	Some college	6 (12.8%)	3 (8.6%)	25 (12.0%)	29 (9.6%)	
	College graduated and above	1 (2.1%)	3 (8.6%)	17 (8.1%)	28 (9.2%)	
Presentation	**Psychotic symptoms**	35 (74.5%)	27 (77.1%)	116 (55.5%)	91 (30.0%)	0.000
	Mood symptoms	19 (40.4%)	15 (42.9%)	94 (45.0%)	145 (47.9%)	0.745
	Suicide ideation	14 (29.8%)	12 (34.3%)	99 (47.4%)	201 (66.3%)	0.000
	Suicide attempt	1 (2.1%)	1 (2.9%)	18 (8.6%)	30 (9.9%)	0.196
	Agitation	20 (42.6%)	20 (57.1%)	57 (27.3%)	54 (17.8%)	0.000
	Aggression before admission	17 (36.2%)	6 (17.1%)	31 (14.8%)	29 (9.6%)	0.000
	Aggression in hospital	21 (44.7%)	12 (34.3%)	57 (27.3%)	50 (16.5%)	0.000
PRN medications for agitation or aggression mean (SD)		2.87 (6.27)	2.02 (3.28)	1.44 (2.8)	.53 (1.55)	0.000
Diagnosis	**Schizophrenia**	14 (29.8%)	6 (17.1%)	34 (16.3%)	38 (12.5%)	0.000
	Schizoaffective	12 (25.5%)	14 (40.0%)	43 (20.6%)	26 (8.6%)	
	Bipolar	2 (4.3%)	3 (8.6%)	20 (9.6%)	22 (7.3%)	
	MDD	1 (2.1%)	1 (2.9%)	0 (0%)	8 (2.6%)	
	Unspecified psychosis	11 (23.4%)	9 (25.7%)	27 (12.9%)	30 (9.9%)	
	Unspecified depressive	6 (12.8%)	2 (5.7%)	75 (35.9%)	169 (55.8%)	
	Others	1 (2.1%)	0 (0%)	10 (4.8%)	10 (3.3%)	
First episode		3 (6.3%)	2 (5.7%)	14 (6.7%)	21 (7%)	0.992
Medications	**No meds**	7 (14.9%)	3 (8.6%)	60 (28.7%)	109 (36.0%)	0.000
	Antipsychotics	17 (36.2%)	11 (31.4%)	41 (19.6%)	52 (17.2%)	
	Mood stabilizer/antidepressants	2 (4.3%)	1 (2.9%)	31 (14.8%)	67 (22.1%)	
	Antipsychotic+mood stabilizer/ antidepressants	21 (44.7%)	20 (57.1%)	70 (33.5%)	57 (18.8%)	
	Others	0 (0%)	0 (0%)	7 (3.3%)	17 (5.6%)	
Antipsychotic equivalent dose of Haldol		10.85 (8.69)	11.28 (7.42)	6.06 (7.50)	3.52 (6.35)	0.000
Length of stay		15.44 (17.24)	16.82 (11.72)	12.24 (10.23)	11.68 (12.67)	0.038

both were significantly higher than SC-MJ+ and SC-MJ- subjects ($p<0.000$ for both).

The length of hospital stay was also significantly different among study groups, with SC+MJ- individuals having the longest length of stay (mean: 16.82, SD: 11.72).

Agitation and aggressive behaviors

151 (25.4%) patients had agitation and 140 (23.5%) patients had aggressive behaviors over their course of hospitalization. Agitation frequency was significantly different between study groups ($p<0.000$), such that SC+MJ- subjects exhibited significantly greater agitation (OR: 4.39, 95% CI: 2.18–8.82), followed by the SC+MJ+ group (OR: 2.51, 95% CI: 1.37–4.59). SC-MJ+ did not show significant agitation. Aggressive behaviors also differed among study groups ($p<0.000$) with SC+MJ+ showing the most significant positive association with aggression (OR: 3.10, 95% CI: 1.67–5.60). The number of PRN medications for severe agitation and aggressive behaviors also revealed a significant group difference ($p<0.000$), with the highest number in SC+MJ+ subjects (mean: 2.93, 95% CI: 1.13–4.74) and no significant differences between other groups.

Table 4. Comparison of the lifetime and current use of other substances in study groups based on self-report and laboratory results.

	SC^+MJ^+		SC^+MJ^-		SC^-MJ^+		SC^-MJ^-		P-value	
	Lifetime	Current	Lifetime	Current	Lifetime	Current	Lifetime	Current	Lifetime	Current
Alcohol	24 (50.0%)	17 (35.4%)	19 (54.3%)	11 (31.4%)	133 (63.9%)	112 (53.6%)	236 (78.1%)	196 (64.9%)	0.000	0.000
Cocaine	19 (40.4%)	11 (22.9%)	16 (45.7%)	8 (22.9%)	99 (47.8%)	82 (29.2%)	180 (59.6%)	132 (43.7%)	0.011	0.008
Benzodiazepines	5 (10.6%)	6 (12.5%)	2 (5.7%)	4 (11.4%)	32 (15.5%)	35 (16.7%)	66 (21.9%)	80 (26.5%)	0.025	0.008
Opiates	8 (17.0%)	5 (10.4%)	8 (22.9%)	2 (5.7%)	59 (28.5%)	39 (18.7%)	126 (41.7%)	74 (24.5%)	0.000	0.011
Amphetamine	4 (8.5%)	2 (4.2%)	3 (8.6%)	1 (2.9%)	21 (10.1%)	18 (8.6%)	29 (9.7%)	24 (7.9%)	0.982	0.514
PCP	3 (7.1%)	2 (4.2%)	3 (8.8%)	1 (2.9%)	10 (4.8%)	10 (4.8%)	9 (3.0%)	9 (3.0%)	0.218	0.746
Ecstasy	0 (0%)	0 (0%)	2 (5.7%)	1 (2.9%)	15 (7.3%)	7 (3.4%)	8 (2.7%)	2 (.7%)	0.039	0.087

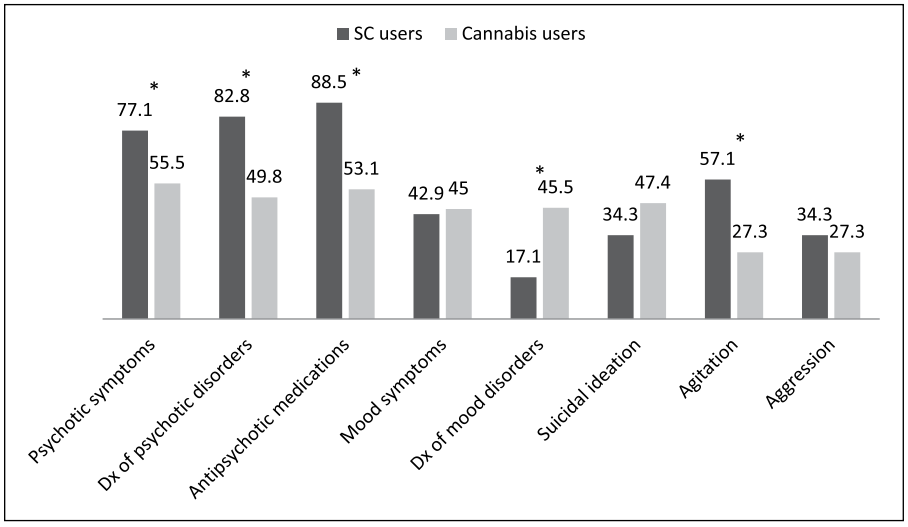

Figure 1. Clinical presentations (as percentage) in SC^+MJ^- and SC^-MJ^+ patients (*: p-values<0.01).

Comparing SC users (MJ-SC+) vs cannabis users (MJ+SC-)

SC users were not significantly different from cannabis users in age, gender, marital status, residential condition, and education. The only demographic factor which differed was ethnicity. SC users had significantly more African American ethnicity (p<0.001). SC users also used significantly less alcohol (p=0.012), less cocaine (p=0.045), and less opiates (p=0.040) compared to cannabis users. Use of other substances did not differ between the two groups.

SC users had significantly different clinical presentation compared to cannabis users. They had more psychotic symptoms (p=0.012) and more agitation (p<0.001). They, overall, were more often diagnosed with any psychotic disorder (p<0.000) and less often diagnosed with mood disorders (p<0.001), more were discharged on antipsychotic medications (p<0.003) with higher equivalent doses of Haldol (p<0.000). They also had a longer hospitalization course (p=0.017) (Figure 1).

Psychosis, agitation, and aggression in study groups controlling for confounders

As shown in Table 5, which summarizes the regression analyses, the association of SC and cannabis use with the dependent variables remained significant even after controlling for potential confounders such as other substance use. In the first and second logistic regression models, with the psychotic symptoms and diagnosis of any psychotic disorder as the dependent variables, respectively, SC^+MJ^+, SC^+MJ^-, and SC^-MJ^+ patients all had significant odds ratios (range on average 1.87–7.24) compared to the SC^-MJ^- reference group, indicating increased risk in association with cannabinoid use (Table 5). In the third model, with agitation as the dependent variable, only SC^+MJ^- patients had significantly higher odds (OR 3.116; CI 1.379–7.040) compared to the SC^-MJ^- group (Table 5). In the final model, with aggression as the dependent variable, only SC^+MJ^+ patients had significantly increased risk (OR 2.27; CI 1.085–4.491) compared to the SC^-MJ^- reference group (Table 5).

Discussion

The clinical data examined in this study indicate that the psychiatric presentation of inpatient SC users is characterized by greater psychotic symptoms as determined specifically by objective signs of psychosis, diagnosis of psychotic disorders, and prescription of antipsychotic medications, which were all significantly more frequent than in cannabis users. The association between psychosis and SC use remained strong even after statistical adjustments for demographic factors or the use of other

Table 5. Multivariate analyses: study groups as the independent variables and psychotic symptoms, diagnosis of any psychotic disorders, agitation, and aggression as dependent variables, controlling for age, gender, ethnicity, and use of other substances.

		Psychotic symptoms		Diagnosis of psychosis		Agitation		Aggression	
		OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
SC^-MJ^- (Reference)		–	–	–	–	–	–	–	–
SC^+MJ^+		3.910	1.800–8.493	5.796	2.522–13.323	1.724	0.831–3.576	2.207	1.085–4.491
SC^+MJ^-		4.108	1.664–10.144	7.274	2.655–19.931	3.116	1.379–7.040	0.968	0.612–1.532
SC^-MJ^+		2.256	1.475–3.452	1.870	1.214–2.880	1.056	0.647–1.722	1.074	0.469–3.630
Methadone		1.332	0.504–3.522	0.840	0.298–2.368	0.492	0.106–2.281	1.358	0.508–3.630
Alcohol		0.596	0.404–0.880	0.845	0.567–1.258	0.810	0.531–1.236	0.531	0.357–0.791
Opiate		0.543	0.320–0.920	0.653	0.381–1.117	0.701	0.377–1.303	1.170	0.685–2.000
Cocaine		0.694	0.470–1.024	1.220	0.822–1.811	0.825	0.534–1.273	0.724	0.483–1.087
BNZD		0.428	0.254–0.721	0.418	0.244–0.715	0.876	0.488–1.573	0.629	0.363–1.091
Amphetamine		1.792	0.866–3.708	1.788	0.857–3.728	1.633	0.780–3.419	0.683	0.316–1.478
MDMA		4.705	1.047–21.138	2.084	0.509–8.540	1.357	0.308–5.971	1.714	0.387–7.592
PCP		0.956	0.376–2.435	1.307	0.493–3.466	0.682	0.212–2.187	0.739	0.266–2.048
Age		0.993	0.997–1.010	0.996	0.980–1.013	0.974	0.956–0.992	0.979	0.963–0.996
Gender		1.055	0.686–1.623	1.300	0.836–2.021	1.048	0.657–1.673	1.699	1.072–2.693
Ethnicity	**Caucasian (Reference)**	–	–	–	–	–	–	–	–
	AA	2.388	1.482–3.848	3.527	2.190–5.683	2.305	1.350–3.935	2.231	1.361–3.655
	Hispanic	1.684	1.038–2.733	1.472	0.900–2.408	1.252	0.708–2.215	1.071	0.638–1.800
	Asian	0.411	0.037–4.591	0.517	0.044–6.133	0.768	0.068–8.659	0.000	0.000

substances. Gaining insights about the psychiatric comorbidity associated with SC use is important, given recent attempts to help reduce and treat the growing population of individuals who consume these potent synthetic cannabimimetic drugs.

As expected, patients within the Dual Diagnosis unit had a positive association between the use of natural cannabis and psychosis, even in the absence of SC, which has been well established clinically and documented in several epidemiological studies and meta-analyses (Burns, 2013; Gage et al., 2016; Van Winkel and Kuepper, 2014). The association between psychosis and cannabis has been consistent in many epidemiological investigations with a modest strength and dose-dependent relationship (McLaren et al., 2010; Wilkinson et al., 2014). The acute psychotic symptoms following cannabis use are usually transient, and disappear when cannabis use stops for most individuals (D'Souza et al., 2009). Psychotic symptoms can, however, extend beyond the period of intoxication following cannabis use, which has been attributed to high potency cannabis (high THC/low CBD levels) (Di Forti et al., 2015) or due to its use in at-risk individuals, such as those with a prior history of psychosis or who have an underlying vulnerability potentially linked to genetics and/or early environmental factors (McLaren et al., 2010). Although psychosis was of significant clinical concern, with 55.5% of cannabis users presenting with psychotic symptoms, a large percentage of SC^-MJ^+ patients were diagnosed with co-occurring depression (45.5%). This high incidence of affective symptoms is consistent with similar comorbidity reported between cannabis use and mood disorders (Lev-Ran et al., 2013). In contrast, SC users had far fewer depression indications (only 17.5%), with psychosis being the prominent clinical presentation.

Most of the data accrued to date regarding SC has focused on its acute intoxication, which has been associated with alarming increases in emergency room visits and calls to poison control centers. Several reports document psychotic presentations after SC use, including acute psychosis, persistent psychotic disorder, and relapse/worsening of a pre-existing psychosis (Castaneto et al., 2014; Glue et al., 2013; Papanti et al., 2013; Spaderna et al., 2013). An online survey of 14,966 participants, reported more paranoia in SC users than in cannabis users (Winstock and Barratt, 2013) which was also reflected in a retrospective review of Texas Poison Control Centers, which reported five times greater percentage of psychotic symptoms in SC compared to cannabis users (Forrester et al., 2012). Moreover, the psychotic presentations following SC use appears to have more agitation and aggressive behaviors compared to cannabis use (Hermanns-Clausen et al., 2013; Kamijo et al., 2014; Papanti et al., 2013). Our current inpatient findings in the post-acute intoxication phase extend the previously published acute observations, emphasizing that the symptoms of psychosis, agitation, and irritability persist for many days and contribute to the need for longer hospital care. It will be important to monitor SC users years after their final drug consumption to determine whether psychiatric impairments may persist and incur long-term mental health, medical, and social burdens.

Various neurobiological theories have been proposed to account for the underlying pathophysiology contributing to cannabinoid-associated psychosis. Since SC compounds affect the same receptors as THC, but with greater potency and efficiency, higher psychotic presentations with SC use suggests that endocannabionoid receptors play a major role in the association with psychosis. The cannabinoid type-1 receptor (CB1R) is one of the most abundant G-protein-coupled receptor in the central nervous system (Herkenham et al., 1991) and is highly expressed in regions of the human brain such as the cerebral cortex, striatum, and hippocampus (Glass et al., 1997; Wang et al., 2003), which are highly implicated in cognition and behavioral features of psychosis pathology. One of the major roles of the endocannabinoid

system is in stress response, and multiple lines of evidence have also suggested that psychosis is associated with impaired stress reactivity (Holtzman et al.. 2013; Mizrahi, 2016; Myin-Germenys and van Os, 2007). The endocannabinoid system has a prominent stress-inhibitory role (Morena et al., 2016), and reduced perceived stress is the most frequently reported reason for cannabis use (Hyman et al., 2009). However, chronic repeated cannabis exposure results in down regulation of the endocannabinoid system and induces abnormalities in stress response, which may influence psychosis risk in vulnerable individuals (Appia-Kusi et al., 2016).

In addition to cannabinoid receptors, dopamine dysregulation is posited as a final common pathway of psychosis, and CB1Rs located adjacent to dopamine neurons in the midbrain indirectly modulate dopaminergic firing activity and subsequently dopamine release in forebrain regions (Riegel and Lupica, 2004). Preclinical studies have clearly demonstrated that THC increases dopamine levels in the prefrontal cortex, ventral striatum (nucleus accumbens), and dorsal striatum (Sami et al., 2015). However, such findings are more controversial in human studies, with modest THC effects reported for the dopaminergic system in the human brain (Sami et al., 2015). Other theories posited to explain the role of the endocannabinoid system in psychosis involve the interactions of the CB1R with GABAergic and glutamatergic neurons, which are strongly implicated in schizophrenia (D'Souza et al., 2009). The highly potent agonist actions of SC compounds would thus be expected to induce robust effects on these convergent neurotransmitter systems regulated by the CB1R and contribute to the strong association of SCs with psychosis.

One of the alternative and highly debated theories for the association between psychosis and cannabinoid use is the "self-medication" of negative symptoms, anxiety, or dysphoria (Van Amsterdam et al., 2015). However, it is less likely that this theory can explain the stronger association of SC use and psychosis compared to cannabis. Indeed, many SC users, such as those in our study, report experiencing anxiety and paranoia after SC use, so it does not appear to alleviate, but instead to exacerbate, such symptoms (Gage et al., 2016; Winstock and Barratt, 2013). Interestingly, a survey of 2513 SC users reported that the vast majority (93%) of participants who reported ever use of cannabis and SC drugs preferred natural cannabis to SCs for inducing greater pleasurable effects when high and being able to function better after consumption. The minority who preferred SC to cannabis reported availability, cost, and the fact that they are not as easily detected in urine tests, among their reasons (Winstock and Barratt, 2013). As such, psychotic patients in the current findings might have used those drugs more because they are cheaper and more easily available, which would be of significant consideration for psychotic patients, who often have functional and resource limitations. Future studies are needed to identify what specific contribution cognitive function, reward sensitivity, or negative affect might play in cannabinoid users who choose SC over natural cannabis.

Another important finding of our study was the higher agitation experienced by SC users, which is consistent with preliminary reports. A case series of 29 patients with documented use of SCs reported pronounced agitation which was more specific to SC compared to cannabis use (Hermanns-Clausen et al., 2013). One explanation for this agitation could be due to the fact that SC compounds lack CBD, which has anxiolytic effects (Iseger and Bossong, 2015). On the other hand, it is important to note that though all SC compounds bind to cannabinoid receptors, their chemical structures differ from THC, so they could affect other receptors as well. For example, it is suggested that the indole structure of a group of these substances may interact with serotonin receptors (Elsohly et al., 2014). It is also evident that while THC in animal models does not produce strong self-administration behavior, SC compounds have been shown to reinforce self-administration in animals, and severe withdrawal symptoms were reported both in animals and humans following their discontinuation (Fattore et al., 2001, 2007). These effects could be explained with SCs' high potency and affinity at CB1Rs (Fantegrossi et al., 2014). A recent study reported that the most common withdrawal symptoms in 20 patients who were admitted for inpatient SC detoxification were agitation (89%) and irritability (83%) (Macfarlane and Christie, 2015). It is thus possible that higher agitation in our SC users in our inpatient population was reflective in part of withdrawal symptoms.

Limitations

Our study was a retrospective review of patients' charts and has all the limitations of such studies. There was no structured scale for the patients' clinical signs and symptoms, thus we could not systematically address the severity of symptoms. However, we used all available data to evaluate patients' presentations and did not limit ourselves to just one specific clinical document, such as discharge summaries. Our data on SC use was based on patients' self-reports and we had no laboratory result to provide information about the specific SC compounds consumed, which vary in potency and chemical structure. As was mentioned, not being detectable in routine drug screening tests is one of the reported motivations for SC use (Gunderson et al., 2014), so it is quite possible that patients under-report their SC use, and we could not comment on the presentations of SC users who denied its use. There is also a potential selection bias since SC-using patients denying such use may have been admitted to general psychiatric wards instead of the dual diagnosis unit. However, even if under-reported, the data still showed clear significant differences between those with and without a positive self-report of SC use. Additionally, we did not have enough data to quantify amount and frequency of each patient's history of use, or to distinguish the full course of withdrawal symptoms. Prospective studies with more details regarding patients' substance use and clinical presentations are needed to address these limitations. It is also important to note that our cohort were from an inpatient unit, which means that these patients possibly had more severe symptoms or other comorbid psychopathologies that led to hospitalization. In addition, our population was mostly unemployed, and more than 40% were homeless. Caution should be taken in generalizing the current results to SC users in outpatient settings or non-psychiatric populations and with a different socioeconomic status.

Conclusion

In this study we observed that SC use was strongly associated with more psychotic presentations and agitation compared to cannabis use. SC users were more frequently diagnosed with any psychotic disorder, needed higher doses of antipsychotic medications, and required longer hospitalizations. Though our study, by its retrospective nature, cannot prove the causal role of SC use in

psychosis comorbidity, our findings do suggest an important association with SC use, which is independent of sociodemographic factors and use of other substances. Given the exponential increase in the prevalence of SC use in the United States and other Western countries, particularly in young adults, the strong association between SC use and psychosis has important implications for current discussions regarding the adverse medical and public health consequences of these cannabimimetic agents.

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