Hospital Stay in Synthetic Cannabinoid Users With Bipolar Disorder, Schizophrenia, or Other Psychotic Disorders Compared With Cannabis Users

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ABSTRACT. Objective: The use of synthetic cannabinoid (SC) products has become popular in recent years, but data regarding their impact on hospital stays are limited. The impact of SC and cannabis use on hospital length of stay and doses of antipsychotics at discharge was assessed in this study. **Method:** The sample consisted of inpatients with discharge diagnoses of bipolar disorder, schizophrenia, or other psychotic disorders. Medical records of patients with self-reported SC use and negative urine drug screens (SC group, $n = 77$), with cannabis use confirmed by urine drug screen (cannabis group, $n = 248$), and with no drug use confirmed by urine drug screen (no-drug group, $n = 1,336$) were examined retrospectively. **Results:** Length of stay (mean [SD] days) significantly differed ($p < .001$) among the SC (8.29 [4.29]), cannabis

(8.02 [5.21]), and no-drug groups (10.19 [9.08]). Antipsychotic doses (chlorpromazine milligram equivalent doses) also significantly differed ($p = .002$) among the SC (254.64 [253.63]), cannabis (219.16 [216.71]), and no-drug groups (294.79 [287.85]). Unadjusted and adjusted pairwise comparisons showed that the cannabis group had a shorter length of stay ($p < .001$) and received lower doses of antipsychotics ($p = .003$) than the no-drug group. SC users did not differ significantly from the other two groups in either length of stay or doses of antipsychotics. **Conclusions:** Our findings suggest that acute SC exposure is not predictive of a more prolonged time for response to antipsychotic medications or of a need for larger doses of these medications compared with cannabis users. (*J. Stud. Alcohol Drugs*, 80, 230–235, 2019)

SYNTHETIC CANNABINOID (SC) products are typically “herbal” mixtures laced with various SC compounds. They are sold around the world under a variety of brand names such as “Spice,” “K2,” and “Kush” and are commonly labeled “not for human consumption” to avoid legal regulations. They have been available in Europe since 2004 (Advisory Council on the Misuse of Drugs, 2014), and JWH-018, a first-generation SC, was first reported in Spice in the United States in 2008 (White House, n.d.). Although the prevalence decreased from 6.5% in 2011 to 3.5% in 2016 per the Monitoring the Future survey (Johnston et al., 2012; Schulenberg et al., 2017), acute SC intoxications have increased significantly in the United States from 2010 to 2015 based on data from the Toxicology Investigators Consortium of the American College of Medical Toxicology (Riederer et al., 2016). The amount of seized SCs also has been increasing worldwide since 2010 (United Nations Office on Drugs and Crime, 2017). The aforementioned findings indicate

continued demand for SCs, with the concomitant negative impact on the health of SC users.

Evidence from epidemiologic research has demonstrated that cannabis may increase the risk of psychosis, although there is no causality established to date (Gage et al., 2016). A meta-analysis that included 35 studies reported a 41% increase in the risk of any psychotic outcome in cannabis ever-users, and there was a dose-dependent effect of cannabis on the risk of psychotic outcome (Moore et al., 2007). More recently, another meta-analysis of 10 studies that included a total of 66,816 individuals confirmed the dose-response relationship between cannabis use and risk of psychosis (Marconi et al., 2016). In addition, daily use, especially of high-potency cannabis, has been reported to be associated with an earlier onset of psychosis (Di Forti et al., 2014).

Although SC use is relatively new compared with cannabis use, reports of associations between SC use and psychosis have been increasing (Celofiga et al., 2014; Fattore, 2016; Khan et al., 2016; Leibu et al., 2013; Sönmez & Köşger, 2016), with the literature largely limited to case reports. In the present study, we compared the impact of SC and cannabis on hospital length of stay and doses of antipsychotics prescribed at discharge in a relatively large inpatient population with bipolar disorder, schizophrenia, or other psychotic disorders.

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Method

Population and setting

Electronic medical records of patients admitted to the University of Texas Harris County Psychiatric Center were examined retrospectively. With 250 beds, the Harris County Psychiatric Center is the largest public inpatient psychiatric facility in Houston, Texas. Inclusion criteria were (a) age 18–65 years; (b) a discharge diagnosis of bipolar I disorder, bipolar II disorder, bipolar disorder not otherwise specified, schizophrenia, schizoaffective disorder, schizophreniform disorder, or brief psychotic disorder based on criteria from the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV; American Psychiatric Association, 1994); and (c) admission between January 2014 and July 2015 (this time frame was chosen because SC use was rarely documented in the electronic medical records before January 2014 and the electronic medical record system at the Harris County Psychiatric Center transitioned to the 10th revision of the *International Statistical Classification of Diseases and Related Health Problems* [ICD-10; World Health Organization, 1992] terminology in August 2015).

Data extracted from electronic medical records included age, gender, ethnicity, urine drug screen results, discharge diagnosis, length of stay, and doses of antipsychotic medications at discharge. Urine drug screen results, including amphetamine, barbiturates, benzodiazepines, cannabinoid, cocaine, methadone, opiates, phencyclidine, and propoxyphene, were determined utilizing immunoassays using urine specimens collected routinely at the time of hospital admission. Doses of antipsychotic medications were converted to chlorpromazine equivalents (Woods, 2003, 2011). The antipsychotic dose at discharge was the dose that the patient required for stabilization during hospitalization, so it was also the dose the patient received during the stay or when it was close to the discharge time if the medication(s) required titration.

Patients were divided into three groups: patients with self-reported SC use and negative urine drug screen (SC group, $n = 77$), patients with no self-reported SC use and positive cannabis use confirmed by urine drug screen (cannabis group, $n = 248$), and patients with no self-reported SC and negative urine drug screen (no-drug group, $n = 1,336$). The University of Texas Health Science Center at Houston Institutional Review Board approved this study.

Statistical analyses

Chi-square, analysis of variance, or Kruskal–Wallis tests, depending on the distribution of data, were used to compare variables among the three groups. Linear regression was used to compare length of stay among the groups while

adjusting for differences in age, gender, ethnicity, diagnosis, and antipsychotic doses at discharge among the three groups. Linear regression also was used to compare antipsychotic doses among the groups while adjusting for differences in age, gender, diagnosis, and length of stay among the three groups. Means are expressed as mean (standard deviation). All significance levels reported are two sided, with $p < .05$ considered statistically significant. Statistical analyses were carried out using IBM SPSS Version 23 (IBM Corp., Armonk, NY).

Results

Demographic and clinical characteristics of the sample

The cohort was composed of 77 patients in the SC group, 248 patients in the cannabis group, and 1,336 patients in the no-drug group. Age at admission and gender were significantly different among the three groups ($p < .001$ for both variables). The discharge diagnosis also was significantly different among the groups ($p = .006$). There was no significant difference in ethnicity among the three groups. The demographic and clinical characteristics of the cohort are summarized in Table 1.

Comparison of length of stay among the three groups

Length of stay among the three groups was significantly different ($p < .001$), with the SC group at a mean of 8.29 (4.29) days, the cannabis group at 8.02 (5.21) days, and the no-drug group at 10.19 (9.08) days. Further pairwise comparison showed that only the cannabis and no-drug groups were significantly different ($p < .001$). Length of stay did not differ between the SC group and cannabis group as well as between the SC group and the no-drug group. Multivariable regression analysis on length of stay obtained after adjusting for age, gender, diagnosis, and antipsychotic doses at discharge gave similar results, remaining significant only between the cannabis and no-drug groups.

Comparison of antipsychotic doses among the three groups

Antipsychotic doses at discharge among the three groups was significantly different ($p = .002$); the mean dose for the SC group was 254.64 (253.63) mg, the cannabis group was 219.16 (216.71) mg, and the no-drug group was 294.79 (287.85) mg. Further pairwise comparison showed that only the cannabis group and no-drug group were significantly different ($p = .003$). Antipsychotic doses did not differ between the SC group and cannabis group as well as between the SC group and the no-drug group. As in the unadjusted analyses, multivariable regression analysis adjusting for age, gender, diagnosis, and length of stay yielded significant results only between the cannabis group and the no-drug group.

TABLE 1. Patient demographics and clinical characteristics

Variable	Cannabis group (<i>n</i> = 248) <i>M</i> (<i>SD</i>) or <i>n</i> (%)	SC group (<i>n</i> = 77) <i>M</i> (<i>SD</i>) or <i>n</i> (%)	No-drug group (<i>n</i> = 1,336) <i>M</i> (<i>SD</i>) or <i>n</i> (%)	<i>p</i>
Age, in years	28.42 (7.68)	32.25 (11.18)	36.33 (12.19)	<.001
Gender				<.001
Male	179 (72.2%)	67 (87.0%)	820 (61.4%)	
Female	69 (27.8%)	10 (13.0%)	516 (28.6)	
Race				.322
White	124 (50.0%)	39 (50.6%)	690 (51.6%)	
Black	124 (50.0%)	38 (49.4%)	629 (47.1%)	
Asian	0 (0)	0 (0)	17 (1.3%)	
Diagnosis				.006
Bipolar I disorder	43 (17.3%)	8 (10.4%)	217 (16.2%)	
Bipolar disorder NOS	86 (34.7%)	25 (32.5%)	330 (24.7%)	
Bipolar II disorder	6 (2.4%)	0 (0)	22 (1.6%)	
Brief psychotic disorder	2 (0.8%)	0 (0)	7 (0.5%)	
Schizophreniform disorder	10 (4.0%)	3 (3.9%)	24 (1.8%)	
Schizoaffective disorder	57 (23.0%)	21 (27.3%)	383 (28.7%)	
Schizophrenia	44 (17.7%)	20 (26.0%)	353 (26.4%)	
Antipsychotic doses, mg	219.16 (216.71)	254.64 (253.63)	294.79 (287.85)	.002*
Length of stay, days	8.02 (5.21)	8.29 (4.29)	10.19 (9.08)	<.001**

Notes: *M* = mean; *SD* = standard deviation; SC = synthetic cannabinoid; NOS = not otherwise specified. *P* value for comparisons among groups based on analysis of variance, Kruskal–Wallis test or chi-square test as appropriate. *Pairwise comparison showed that only the cannabis group and no-drug group was significantly different (*p* = .003). **Pairwise comparison showed that only the cannabis and no-drug groups were significantly different (*p* < .001).

Discussion

The present study examined length of hospital stay and antipsychotic doses at discharge among individuals with SC use, cannabis use, and no drug use. Patients with cannabis use had shorter hospital stays and received lower doses of antipsychotic medications compared with patients with no drug use. Consistent with our results, Grace et al. (2000) reported that patients with urine drug screen positive for tetrahydrocannabinol (THC) with psychosis were younger and had shorter stays than those with negative results, although their results did not reach statistical significance, which may be because of the small sample size. The authors also found that those who screened positive for THC and had psychosis relapsed more frequently.

Consistent with our results, Johnson et al. (2016) reported that cannabis use was associated with a shorter length of stay in patients with a discharge diagnosis of bipolar disorder, schizophrenia, schizoaffective disorder, or psychosis not otherwise specified. Similar results were reported by Schmidt et al. (2011), who found that patients with dual diagnoses of substance use and schizophrenia had shorter hospitalizations, but they also used emergency services more often and were admitted more often. They also had worse prognoses than those without co-occurring substance use. A systematic review that included 13 longitudinal studies corroborated the findings that cannabis use in patients with psychosis was associated with increased relapse (Zammit et al., 2008). Johnson et al. (2016) also found that patients with bipolar disorder and cannabis ex-

posure had more episodes of agitation and required more monitoring and interventions during the period of hospitalization, despite having a shorter hospital stay. This led to another hypothesis that the psychotic exacerbation with cannabis exposure may differ from the relapse of a primary psychotic disorder. The exacerbation in the presence of cannabis may be driven by the effect of cannabis, which is distinct from the natural relapse of their primary mental illnesses. This may explain the quicker remission and lower antipsychotics at discharge since the substance-induced exacerbation may be a less severe relapse than a true relapse of the primary psychotic disorder.

Interestingly, cannabis users had shorter stays and lower antipsychotic doses compared with no-drug users, whereas the SC users did not show these differences. A possible mechanism is that cannabis products contain some protective component(s) that SCs do not have, such as the antagonist effects of THC at higher doses and other components of cannabis, such as cannabidiol, which has antipsychotic effects (Zuardi et al., 2012).

Although patients using SC had more severe psychiatric symptoms at their acute clinical presentation, as others have described (Bassir Nia et al., 2016), the SC group had a hospital stay similar to cannabis users. The underlying mechanisms of this finding are unknown. There are similarities and differences between SC and delta-9-tetrahydrocannabinol (Δ^9 -THC), the principal psychoactive component of plant-derived cannabis. Both SC and Δ^9 -THC bind to type 1 and 2 cannabinoid receptors (CB1R and CB2R), with CB1R predominantly located in the central nervous system and

contributing to central nervous system effects, whereas CB2Rs are more peripherally distributed. Δ^9 -THC is a partial agonist of the CB1R, whereas most SCs are full agonists.

There are many different SC products on the market. SC compounds have more potent affinities for CB1Rs and CB2Rs and intrinsic activities than Δ^9 -THC (Atwood et al., 2010; Demuth & Molleman, 2006; Grigoryev et al., 2011; Kapur et al., 2009; Martín-Calderón et al., 1998; Rinaldi-Carmona et al., 1996; Vardakou et al., 2010). Each compound may be further metabolized to different active metabolites (Brents et al., 2011; Chimalakonda et al., 2012; Wintermeyer et al., 2010). Furthermore, different SC molecules have different affinities. Other than the endocannabinoid pathway, other neurotransmitter systems such as dopamine may also be involved in the effects of SCs (Riegel & Lupica, 2004; Sami et al., 2015). Some effects of SCs mimic those of Δ^9 -THC, such as relaxation, elevated mood, altered perception, and psychotomimetic effects, although the higher potency of SCs at CB1Rs produces stronger psychotomimetic effects (National Institute on Drug Abuse, 2015). Current understanding of the impact of SC use on psychosis is far from comprehensive as compared with the effect of Δ^9 -THC. Although both SC and cannabis can induce psychosis, the psychotomimetic effects of SCs are more prominent (Bassir Nia et al., 2016; Glue et al., 2013). In addition, the unique effects of SCs include kidney injury, seizures, suicidal ideation, and fatality. The relatively lesser prominence of psychosis associated with Δ^9 -THC in comparison with SCs could be at least partially attributable to the antipsychotic component, cannabidiol, in cannabis but not in SC products. These results emphasize the need for clinicians to educate patients to be abstinent from certain substances, especially in those with a history of psychoses.

Inconsistent results also have been reported. A recent similar chart-review study found that SC users had longer stays and received higher doses of antipsychotics than did cannabis users (Bassir Nia et al., 2016). The differences between their study findings and our results may be explained by differences in the patient cohorts studied. Bassir Nia et al. reviewed the electronic medical records of all patients with admission diagnoses including psychotic disorders, depressive and bipolar disorders, and other diagnoses. Furthermore, a significant proportion of the cannabis and control groups included individuals with depressive disorders, whereas our study comprised only patients with schizophrenia spectrum and bipolar disorder. Our group recently published findings indicating that patients with psychotic disorders with self-reported SC use had shorter lengths of stay and received lower doses of antipsychotics compared with those who did not have SC exposure before admission (Deng et al., 2018). However, in the present study we did not find differences between the SC group and the no-drug group on these two measures. We speculate that the reason for this is that we matched patients by age, gender, ethnicity, and diagnosis

in the previous study. Therefore, both groups of patients may have used other substances. This differs from how we controlled for other substance use in the present study by using both self-reports and urine drug screen results. The synergistic effect of SC when used in combination with other substances might contribute to the different psychotomimetic effects for SC and cannabis alone.

The present study is a retrospective review of patients' electronic medical records, with the inherent limitations of such research. It was not a randomized controlled trial. Hence, the three groups are not similar in terms of demographics and patient characteristics. However, we controlled for potential confounders in the multivariate regression models. Structured interviews such as the commonly used Structured Clinical Interview for DSM-IV (First et al., 1995) were not used for diagnosis, and structured scales for clinical signs and symptoms were not applied. However, we used two important clinical indices—length of stay and antipsychotic doses—as markers for the intensity and persistence of patients' clinical symptoms. We did not have longitudinal data on the patients because of the cross-sectional nature of the present study, and this issue should be explored in future studies.

Conclusion

The present study indicates that cannabis users with comorbid bipolar disorder, schizophrenia, or other psychotic disorders may require lower doses of antipsychotics and have shorter hospital stays than the no-drug group. Furthermore, despite their more prominent psychotic symptom presentations, as consistently reported by other studies, we found that SC users did not differ from cannabis users in their doses of antipsychotic medications and length of hospital stay. Although plant-derived cannabis and synthetic cannabinoids share similar binding affinities to CB1Rs, there are differences in their pharmacology that may account for disparities in their clinical effects. Prospective studies are needed to develop personalized treatments for individuals with SC use disorder and to determine the long-term effects of SC use on the brain.

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