Neuropsychiatric Sequelae in Adolescents With Acute Synthetic Cannabinoid Toxicity

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abstract

BACKGROUND AND OBJECTIVES: Adolescents represent the largest age group that presents to emergency departments (ED) for synthetic cannabinoid (SC) toxicity; however, the neurotoxic effects of acute SC exposures in this group are understudied. Our aim was to characterize the neuropsychiatric presentation of adolescents with SC-related exposure in the ED compared with those with traditional cannabis exposure.

METHODS: A multicenter registry of clinical information prospectively collected by medical toxicologists (Toxicology Investigators Consortium Case Registry) was reviewed for adolescents presenting to the ED after SC or cannabis exposure from 2010 through 2018. Associations were measured between drug exposures and neuropsychiatric symptoms and/or signs. Exposures were classified into 4 groups: SC-only exposure, SC-polydrug exposures, cannabis-only exposure, and cannabis-polydrug exposures.

RESULTS: Adolescents presenting to the ED with SC-only exposure ($n = 107$) had higher odds of coma and/or central nervous system depression (odds ratio [OR] 3.42; 95% confidence interval [CI] 1.51–7.75) and seizures (OR 3.89; 95% CI 1.39–10.94) than those with cannabis-only exposure ($n = 86$). SC-only drug exposure was associated with lower odds of agitation than cannabis-only exposure (OR 0.18; 95% CI 0.10–0.34). In contrast, the group with SC-polydrug exposures ($n = 38$) had higher odds of agitation (OR 3.11; 95% CI 1.56–7.44) and seizures (OR 4.8; 95% CI 1.80–12.74) than the cannabis-polydrug exposures group ($n = 117$).

CONCLUSIONS: In this multisite cohort of US adolescents assessed in the ED, SC exposure was associated with higher odds of neuropsychiatric morbidity than cannabis exposure providing a distinct neurospychiatric profile of acute SC toxicity in adolescents.

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Drs Anderson and Manini conceptualized and designed the study, conducted all data analyses, coordinated and supervised data collection, and drafted the manuscript; Ms Oprescu and Dr Hurd reviewed collected data, organized data into specific data sets, assisted with designing the study, and identified data to be analyzed; Dr Dayan assisted in the conceptualization and design of the study; Drs Calello and Monte provided access to the Toxicology Investigators Consortium Case Registry and provided data for analysis; and all authors reviewed and revised manuscript, approved the final manuscript as submitted, and agree to be accountable for all aspects of the work.

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WHAT'S KNOWN ON THIS SUBJECT: Adolescents are the largest age group presenting to emergency departments for acute synthetic cannabinoid (SC) toxicity, with these visits requiring more ICU-level care than those in adults.

WHAT THIS STUDY ADDS: This study details the severe neuropsychiatric sequelae related to acute SC toxicity in adolescents compared with those related to cannabis. Different neuropsychiatric toxicities were identified when SC was used as a single agent or with other illicit substances.

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Synthetic cannabinoids (SCs) have garnered international attention due to their popularity, accessibility, and demands on health care use.[1,2] Initially, SCs were created for their cannabimimetic activity; however, because of their psychotropic effects from potent agonism of cannabinoid receptor 1 (CB1) and cannabinoid receptor 2, SCs are now primarily used recreationally.[3,4] The strong affinity of SC to CB1 is postulated to cause prolonged neuropsychiatric toxicity and have a higher addictive potential than naturally sourced CB1 agonists, namely tetrahydrocannabinol.[4–6] Reported adverse effects of SC toxicity include tachycardia, cardiac ischemia, acute kidney injury, agitation, first episode of psychosis, seizures, and death.[3,7] Furthermore, relative to cannabis toxicity in the adult emergency department (ED) population, pediatric SC-related poisonings have more significant clinical cardiotoxicity and neurotoxicity.[8] Similar cardiac and neurologic symptoms were reported in a recent study of adolescents presenting to the ED with SC-related poisonings.[9] Despite these adverse effects, the prevalence of reported poisonings due to SC use have risen since 2011 with upward trends reported through 2015.[1,10–12] In parallel, the number of patients across all age groups seeking emergency medical treatment of SC toxicity is reported to be 30 times that of cannabis-associated visits.[7,13]

Although recent data from the 2017 Youth Risk Behavioral Surveillance System support declining usage of SC in adolescents,[11] this population remains the largest age group to present to EDs for SC exposures.[14] Smaller case series of European adolescents seen in the ED for SC intoxication support that adolescents require more ICU-level care,[15] have higher rates of psychiatric symptoms, and have longer recovery times compared with those seen for cannabis.[13] However, larger studies in the United States have not examined the acute neuropsychiatric toxicities associated with SC use in adolescents. Therefore, our aim was to characterize the neuropsychiatric presentation of adolescents to the ED after SC exposure compared with that of cannabis exposure.

METHODS

Data Sources

This was a multicenter registry analysis spanning January 2010 through September 2018 of a cohort of adolescent patients reporting to the Toxicology Investigators Consortium (ToxIC). This consortium maintains a core case registry in which participating sites agree to record all case patients seen at local hospitals and EDs where a consultation by a medical toxicologist was requested to aid clinical care. The core registry was established in January 2010, and as of October 1, 2018, it contained >62 000 cases from 23 states, 35 US cities, and 65 US hospitals, representing exposures to >1100 different toxicological agents. The registry collects clinical and exposure information on all patients in a Health Insurance Portability and Accountability Act–compliant, highly secure online registry during hospital encounters from consultations within the ED and/or inpatient settings. All patients in the registry are seen at the bedside by highly trained, board-certified medical toxicologists. Currently, this surveillance system is the only multicenter case registry that contains clinical information obtained at the bedside by physicians with medical toxicology expertise. The exposures described for patients in the ToxIC Case Registry are patient or witness reported. It is likely that the vast majority of adolescent SC exposures had medical toxicology consultation at participating ToxIC EDs, and SC exposures in the registry are not routinely confirmed with bioanalytical testing. A comprehensive description of the ToxIC Case Registry from 2010 to 2017 has been previously published.[16–22] The participating institution's independent review board all approved participation in the registry. The ToxIC Case Registry is also approved by the Western Institutional Review Board. For this study, the investigators received an exemption approval from the Icahn School of Medicine at Mount Sinai Independent Review Board to conduct data extraction and analysis.

Study Protocol

Adolescents aged 13 to 19 were eligible for inclusion in this study on the basis of enrollment into the ToxIC Case Registry with the following characteristics: SC or cannabis exposure, presentation to the ED, and bedside medical toxicology consultation requested by the ED clinical team. Discrete numeric ages were not recorded for every patient because of the categorical manner in which data are collected in the registry; therefore, only patients in the 13- to 19-year-old range were included. All available data regarding deidentified case information for each patient were extracted and organized into a standardized format, including the following variables: age (by range), sex, reported exposure(s), death in hospital, location of toxicology encounter, and neuropsychiatric signs and/or symptoms classified by 6 descriptive characteristics (agitation, coma and/or central nervous system [CNS] depression, seizures, hallucinations, delirium and/or toxic psychosis, and extrapyramidal signs [EPSs]). Route of ingestion was inconsistently reported in the registry. Not included in the registry were length of stay and extent and severity of inpatient illness. Exclusion criterion were if exposure report originated from a service outside of the ED, if cases were outside the range of 13 to 19 years of age, or if there was

concomitant cannabis and SC use ($n = 11$).

Data Analysis

The patients were categorized and analyzed in 4 subgroups: (1) SC-only exposure, (2) SC and other drug exposure (SC-polydrug), (3) cannabis-only exposure, and (4) cannabis and other drug exposure (cannabis-polydrug). We used standard descriptive statistics to summarize the characteristics of the population within these 4 groups. Odds ratios (ORs) with 95% confidence intervals (CIs) were used, with significance set at $P < .05$ to compare drug exposures with neuropsychiatric symptoms. Statistical calculations were performed by using JMP software (SAS Institute, Inc, Cary, NC) and GraphPad Prism 5.0.

RESULTS

Demographics

Of the 415 patients in the 13- to 19-year-old age range with cannabis or SC exposure reported in the registry, 348 were included in our study. The numeric totals are as follows: 107 patients in the SC-only group, 38 in the SC-polydrug group, 86 in the cannabis-only group, and 117 in the cannabis-polydrug group. Male patients outnumbered female patients across all groups (cannabis only 66.3%, SC only 81.3%, cannabis-polydrug use 67.5%, and SC-polydrug use 86.8%). Among the cases included, death occurred in 1 individual from the SC-only cohort.

Single-Drug Exposures

The SC-only group had higher odds of coma and/or CNS depression (OR 3.42; 95% CI 1.51–7.75) and seizures (OR 3.89; 95% CI 1.39–10.94) when compared with the cannabis-only group (Table 1). The odds of agitation, however, were significantly less in SC-only exposures than in the cannabis-only exposures (OR 0.18; 95% CI 0.10–0.34). Between the 2 single-drug exposure groups, there was no significant difference in the odds of delirium and/or toxic psychosis; EPSs, dystonia, and/or rigidity, or hallucinations (Table 1).

Polydrug Exposures

SC-polydrug exposure in adolescents had higher odds of both agitation (OR 3.11; 95% CI 1.56–7.44) and seizures (OR 4.8; 95% CI 1.80–12.74) compared with cannabis-polydrug exposures. No other associations were observed between the polydrug groups and the neuropsychiatric signs and symptoms reported (Table 1).

Coexposures

The most common class of exposure associated with SC use was sympathomimetics, which includes synthetic cathinones, cocaine, amphetamines, and 3,4-methyl enedioxymethamphetamine (44.7%). In the cannabis-polydrug group, sympathomimetics and ethanol were the 2 most common class of drugs, used at a rate of 29.9% (all data shown in Table 2). Sympathomimetic use in the SC-polydrug group was reported at 1.5 times the rate reported in the cannabis-polydrug group, with rates of 45% and 30%, respectively. Ethanol usage was reported 3.8 times less in the SC-polydrug group (7.9%) than the cannabis-polydrug group (29.9%).

DISCUSSION

This study provides insight into the acute neurotoxicity profile of adolescent SC use. Use of SC alone was associated with severe neuropsychiatric signs and symptoms, supported by the higher frequency of both coma and/or CNS depression and seizures in the SC-specific group than in the cannabis-specific exposure cohort. Unlike the SC-only group, which had less agitation than the single-cannabis exposure group, the adolescents in the SC-polydrug group had higher odds of agitation in comparison with the cannabis-polydrug group. Higher odds of agitation in the SC-polydrug group may be related to the increased reported incidence of sympathomimetic drug coexposure in the adolescent SC-polydrug group. These results together offer insight into the expected clinical effects of adolescents with acute SC toxicity and emphasizes the need for targeted public health messaging to adolescents about the dangers of using SC, alone or combined with other substances.

Findings from our study further confirm the previously described association between SC-specific overdose and severe neuropsychiatric outcomes. In the SC-only and SC-polydrug groups, the incidence of seizures was distinctly elevated compared with in the cannabis-only group. Seizures are a frequent and known complication of SC use, with 37 500 seizures attributed to SC exposure in 2014, an increase of 12 times the rate reported in 2010.[1] Animal models have identified that the seizures induced by SCs are potentiated by CB1 agonism and enhanced glutamatergic transmission in the hippocampus.[23] The developing brain is particularly vulnerable to the neurotoxic effects of CB1 overactivation by SCs, leading to aberrations in the neurotransmitters modulating the seizure threshold.[24] Higher odds of seizures in adolescent SC exposures are consistent with previous investigations of the ToxIC Case Registry[12,18,19] and comparable to adult studies on biochemically confirmed SC-related poisonings.[25] Presentation of SC-related seizures appears to be specifically associated with acute toxicity and has not been shown to be a lasting sequela, as shown in 1 case series.[26] Analysis of the SC-only group in our study also identified an increased association with coma and/or CNS depression than in cannabis-only exposures. This observation corroborates findings

TABLE 1 Neuropsychiatric Toxicity of Adolescent SC Exposures Compared With Cannabis Exposures

Neuropsychiatric Sign or Symptom	SC Only, *N* (%)	Cannabis Only, *N* (%)	OR (95% CI)	SC-Polydrug Use, *N* (%)	Cannabis-Polydrug Use, *N* (%)	OR (95% CI)
Agitation	23 (23.5)	54 (62.8)	0.18 (0.10–0.34)***	18 (47.4)	24 (20.9)	3.11 (1.56–7.44)***
Coma and/or CNS depression	28 (28.5)	9 (10.5)	3.42 (1.51–7.75)***	7 (18.4)	30 (26.1)	0.64 (0.26–1.61)
Delirium and/or toxic psychosis	17 (17.4)	10 (11.6)	1.60 (0.69–3.70)	14 (36.8)	28 (24.3)	1.81 (0.83–3.97)
EPS, dystonia, and/or rigidity	2 (2.0)	2 (2.3)	0.88 (0.12–6.35)	1 (2.63)	7 (6.1)	0.42 (0.05–3.50)
Hallucinations	7 (7.1)	13 (15.1)	0.43 (0.16–1.14)	6 (15.8)	13 (11.3)	1.47 (0.51–4.19)
Seizures	19 (19.4)	5 (5.8)	3.89 (1.39–10.94)***	11 (28.9)	9 (7.8)	4.80 (1.80–12.74)***

*** $P < .01$.

from an observational study of adolescents treated in EDs for biochemically confirmed SC poisoning, in which an adolescent population of primarily SC-only users had similar increases in coma.[27] Taken together, seizures and coma and/or CNS depression were unique to the SC-only group, whereas in the SC-polydrug group, the odds of agitation and seizures were significantly increased. This finding underscores the unique neuropsychiatric outcomes for adolescents, especially those with coexposures.

Whereas SC-polydrug exposures were associated with higher odds of agitation compared with the cannabis-polydrug group, the reverse was observed in the SC and cannabis-only groups. The finding of less agitation in the SC-only cohort than in the cannabis-only cohort differs from contemporary adult and adolescent literature on SC-associated agitation.[7,8,12] The discordance in the prevalence of agitation depending on single-agent exposure or coexposures may represent differences in studied populations, with more severe toxicity prompting the ED presentations reported in this study. Furthermore, given that ToxIC Case Registry data are based on consultation by a medical toxicologist, there is also potential for selection bias regarding the types of centers with medical toxicologists affiliated with the ToxIC Case Registry. However, many medical toxicologists work in 1 or more academic medical centers as well as in hospitals in smaller and/or community health care facilities; thus, the reach of ToxIC extends to urban, suburban, and rural areas, which helps preserve the registry's ability to collect community-level adverse-event data associated with SCs and other novel substances. On further examination of the drugs used in both groups, sympathomimetics were reported in the SC-polydrug group at ~1.5 times the rate of the cannabis group. The additive effects of these substances with the previously described sympathomimetic toxidrome of SC may help to explain the increased odds of agitation seen in our SC-polydrug cohort.[10,12,28] Ethanol use also differed notably between the SC- and cannabis-use groups. In the cannabis-polydrug group, ethanol was reported at a rate of 3.8 times more than in the SC-polydrug group. Recent data from the Monitoring the Future Study supported a similar prevalence of ethanol use in ever-SC users and ever-cannabis users.[29] Our findings indicate a possible difference in the acute toxicity profile and usage of ethanol among adolescent SC and cannabis users. In addition, multiple studies have reported that ever usage of SC is significantly associated with ever usage of cannabis[6,30]; however, in our study, the number of those presenting with co-ingestion in the ED was small (11 patients in a sample of 415). The small sample size of

TABLE 2 Characteristics and Coexposures by Group

	SC Only (*N* = 107)		Cannabis Only (*N* = 86)		SC-Polydrug Use (*N* = 38)		Cannabis-Polydrug Use (*N* = 117)	
	n	%	*n*	%	*n*	%	*n*	%
Male sex	87	81.3	57	66.3	33	86.8	79	67.5
Female sex	20	18.7	29	33.7	5	13.2	38	32.5
Coexposure								
Analgesics	—	—	—	—	4	10.53	11	9.40
Anticoagulant	—	—	—	—	1	2.63	0	0.00
Anticholinergic	—	—	—	—	5	13.16	17	14.53
Anticonvulsant	—	—	—	—	1	2.63	0	0.00
Antidepressant	—	—	—	—	5	13.16	8	6.84
Antipsychotics	—	—	—	—	5	13.16	5	4.27
Cardiovascular	—	—	—	—	0	0.00	1	0.85
Cough and cold	—	—	—	—	1	2.63	16	13.68
Ethanol	—	—	—	—	3	7.89	35	29.91
Herbal supplement	—	—	—	—	0	0.00	1	0.85
Nicotine	—	—	—	—	1	2.63	2	1.71
Opioid	—	—	—	—	1	2.63	17	14.53
Psychoactive and/or hallucinogen	—	—	—	—	4	10.53	15	12.82
Sedative-hypnotic	—	—	—	—	2	5.26	20	17.09
Sympathomimetics[a]	—	—	—	—	17	44.74	35	29.91
Unknown	—	—	—	—	2	5.26	4	3.42

—, not applicable.

[a] Amphetamines, cocaine, synthetic cathinone, and 3,4-methylenedioxymethamphetamine.

acute coexposures with cannabis and SC may point to the unique population presenting to the ED because of the acuity of symptoms and does not reflect trends in concurrent past cannabis and SC usage, as shown in previous studies.[6,11,29,31] Overall, these differences in co-ingestion patterns between the SC- and cannabis-polydrug groups define a specific clinical profile for adolescents presenting to the ED with these toxicities.

Our findings provide a strong foundation from which future studies can address key questions left unanswered. First, given the heterogeneity of SCs, identifying the type of SC used by serum or urine analysis and correlating that to the presentation of adolescents in the ED can provide insight to specific toxidromes associated with discrete SC compounds. Second, comprehensive longitudinal data on the long-term effects of adolescent exposure to SC is warranted in clinical populations especially because animal models have shown that early exposure leads to neurocognitive impairments into adulthood.[32] Lastly, additional investigations into the management of adolescent SC toxicity in the ED is warranted given the health care cost burden of SC-related ED visits.[33]

Limitations of the study include the lack of data available in the registry for particular variables, including patient-specific race and/or ethnicity, concurrent illness, previous drug use, and comorbid conditions. The population was male predominant with a sex distribution similar to that of other adolescent SC studies.[6,11] Another limitation is user or witness report of substance exposure and a lack of confirmatory testing for SC. Misclassification bias of substance exposure is minimized by the fact that emergency physicians and medical toxicologists examined each patient at the bedside and reported details of each exposure. Although there are insufficient toxicological data correlating serum or urine SC metabolites with clinical outcomes, self-reports have been shown to be of important value in clinical studies.[34] In addition, it is important to acknowledge the relatively small sample size for each outcome category, although our cohort represents a larger sample size than that previously studied.[9] Finally, our study focused on ED presentation and did not evaluate follow-up after discharge, and as a result, the long-term outcomes are not known. Nevertheless, our findings serve as a foundation for future studies to investigate the neuropsychiatric sequelae of SC toxicity in adolescents.

CONCLUSIONS

In this large multicenter registry of adolescents with SC exposures prompting ED visits, neuropsychiatric morbidity was strongly associated with SC exposure. CNS depression and seizures were more common in single-drug SC exposure, whereas agitation and seizures were the predominant symptoms in polydrug use with SC. Our results contribute additional insight to a specific acute neuropsychiatric toxicity profile of SC exposures in adolescent patients.

ABBREVIATIONS

CB1: cannabinoid 1 receptor
CI: confidence interval
CNS: central nervous system
ED: emergency department
EPS: extrapyramidal sign
OR: odds ratio
SC: synthetic cannabinoid
ToxIC: Toxicology Investigators Consortium

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