Synthetic Cannabinoid Exposure in Adolescents Presenting for Emergency Care

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Objective: The objective of this study was to characterize the clinical picture and management of synthetic cannabinoid exposure in a cohort of adolescents.

Methods: Using the 45 participating sites of the Toxicology Investigators Consortium Registry, a North American database, we conducted an observational study of a prospectively collected cohort. We identified all adolescent (12–19 years) cases of synthetic cannabinoid exposure who have received medical toxicology consultation between January 2012 and December 2016. Clinical and demographic data were collected including age, sex, circumstances surrounding exposure, coingestants, clinical manifestations, treatment, disposition, and outcome.

Results: We identified 75 adolescents who presented to the emergency department with synthetic cannabinoid exposure. Most were male (91%) and between the ages of 16 and 19 (66%). The most common symptoms were neuropsychiatric with 50 adolescents (67%) exhibiting central nervous system (CNS) manifestations. There was no predominant toxidrome, and 9 patients (12%) were mechanically ventilated. Mainstay of treatment was supportive care. No deaths were reported.

Conclusions: Synthetic cannabinoid exposure in adolescents is primarily characterized by CNS manifestations, which are varied and may be life-threatening. Frontline caregivers should maintain a high index of suspicion for synthetic cannabinoids, especially in adolescents who present with unexplained CNS manifestations, as there is no specific toxidrome or confirmatory rapid drug screen to detect them.

Key Words: poisoning, synthetic cannabinoids, adolescents

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Synthetic cannabinoids are manufactured substances designed as cannabinoid CB1/CB2 receptor agonists. There are a variety of different street names used (Table 1) and ever changing chemical formulations. They are 2 to 200 times more potent than alkaloids in marijuana on the cannabinoid receptors, particularly the CB1 receptor, and have an increased risk of neuropsychiatric symptoms.[1–5] Synthetic cannabinoids are presently the second most abused illicit drug class by adolescents in the United States and are dwarfed only by marijuana.[6,7] Importantly, because there is a diverse and ever-changing population of designed molecules with agonist properties at cannabinoid receptors, the clinical effects of these agents can be variable, partially owing to pharmacological interactions with other receptors.

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Synthetic cannabinoids were marketed as "legal highs" in the early 2000s and until recently were easily available on the Internet, in smoke shops, and convenience stores.[4,8,9] In 2011, they were classified by the United States Drug Enforcement Agency as schedule 1 drugs, inferring that they have a high potential for abuse and no accepted medical use.[9] Importantly, synthetic cannabinoid use in youth has been linked with increased likelihood of engaging in violence, injury, other substance abuse, and sexual risk behaviors.[10] Ease of access via the Internet, low price, intense highs, and challenges in detection by routine urine drug screens makes them attractive drugs for abuse.[5,8,11–13] This is reflected in data from United States Poison Control Centers, which report 330% increase in synthetic cannabinoids calls in the first 4 months of 2015.[12] In fact, synthetic cannabinoid exposures requiring medical care have steadily increased between 2010 and 2015, with roughly 30% of exposures reported in the pediatric population.[8,13] Annual prevalence of synthetic cannabinoids among older adolescents has recently been estimated at 5% by the 2015 Monitoring the Future report, a survey of roughly 50,000 adolescents.[7]

At present, only case reports and small case series describing synthetic cannabinoid exposure in the adolescent population are available.[10,14–16] Because of the increasing use of synthetic cannabinoids in the general population and high risk of harm, we decided to examine the characteristics of adolescent synthetic cannabinoid use and toxicity. We sought to examine the characteristics and effects of synthetic cannabinoid exposure in adolescents, by using ToxIC, a large well-established North American toxicosurveillance system.

METHODS

Data Sources

The ToxIC Case Registry was established by the American College of Medical Toxicology in January 2010 and is routinely used to conduct toxicosurveillance research.[8,17–20] ToxIC is currently comprised of 45 sites, mostly across the United States. Participating sites prospectively register all cases managed by medical toxicology services at the bedside into an online, secured database, which is maintained by the American College of Medical Toxicology. Prospectively compiling detailed demographic and clinical data on all cases, the ToxIC database allows for the identification, extraction, and pooling of patient-deidentified information on toxicological exposures across all sites. ToxIC is approved by the Western Institutional Review Board, and sites contribute cases pursuant to the approval, policies, and procedures of their respective institutional review boards.

Patient Cohort

We identified all prospectively collected reports of synthetic cannabinoid exposures in the ToxIC database between January 1, 2012 and December 31, 2016. The following inclusion criteria were used to identify synthetic cannabinoid exposure cases: (1) 12 to 19 years of age and (2) presented to a participating center with a

TABLE 1. Common Street Names of Synthetic Cannabinoids

– K2	– Bizarro	– Orange bud/OJ
– Spice	– Crazy Monkey	– Toochi
– Kush	– Diablo	– Fire
– Black Mamba/Mamba	– Caution	– Mind Trip
– Head Rush 50 X		

history and/or laboratory confirmation of exposure to synthetic cannabinoids.

Exposures in the ToxIC database are characterized by detailed history and physical examination performed by the consulting medical toxicology service at the bedside. Additional laboratory investigations were performed as indicated. Data were tabulated including age, sex, referral source, symptoms, signs, management, disposition, and outcome. Missing data fields were assumed to be a response in the negative, thus leading to a more conservative estimate of variables.

RESULTS

We identified 75 cases of suspected synthetic cannabinoid exposure in adolescents during the study period. The main demographic and clinical characteristics and management strategies are reported in Table 2. Most users were male (91%) and in the older adolescent age range of 16 to 19 years (66%). Fourteen patients (19%) were exposed to more than 1 substance. Over the course of the first 4 years studied, there was an increasing number of reported cases with a maximal number of 27 cases in 2015. There were only 7 cases reported in 2016.

There was no prominent toxidrome in our cohort (Table 2). Vital signs were variable and ranged from tachycardia (n = 12) to bradycardia (n = 8) and from hypertension (n = 2) to hypotension (n = 2). Respiratory depression was reported in 6 patients (8%). The most common clinical manifestations were neuropsychiatric in nature with 67% (n = 50) of cases reporting at least 1 of the following: central nervous system (CNS) depression (n = 22 [29%]), agitation (n = 18 [24%]), delirium (n = 16 [21%]), and seizures (n = 11 [15%]). Five patients (6%) developed acute kidney injury and 4 (5%) developed rhabdomyolysis, 1 of whom required hemodialysis. There were no reported deaths.

The most commonly administered treatments were benzodiazepines (n = 26 [35%]), intravenous fluid resuscitation (n = 23 [31%]), intubation and mechanical ventilation (n = 9 [12%]), and antipsychotics (n = 7 [9%]). Of the 9 patients who were intubated, all were male and 2 were exposed to more than 1 substance (synthetic cathinones and acetaminophen). All 9 intubated patients had at least 1 neuropsychiatric sign: 4 were agitated, 4 had CNS depression/coma, 3 had delirium/toxic psychosis, and 2 had seizures. In addition, 2 of the intubated patients had rhabdomyolysis, 1 of whom developed acute kidney failure requiring hemodialysis.

Patients were largely managed in the emergency department (n = 41 [55%]); however, 19 patients (25%) were admitted to the intensive care unit and 14 adolescents (19%) were admitted to hospital wards.

DISCUSSION

This study describes a large cohort of adolescents exposed to synthetic cannabinoids. Prior work described case reports and small case series,[10,14–16] including a report of 3 adolescents who presented with myocardial infarction after synthetic cannabinoid exposure.[15] Most pediatric patients in our study were older adolescents (66%), with a significant male predominance (91%), and 1 in 8 received mechanical ventilation. The CNS was most commonly affected with 67% of cases displaying at least 1 sign. Management was largely supportive, with benzodiazepines (35%) as the most commonly administered drugs.

Our findings are in line with the adverse effects profile and treatments reported in adults with acute synthetic cannabinoid

TABLE 2. Characteristics of Adolescents Presenting With Synthetic Cannabinoid Exposure Captured in the ToxIC Case Registry

	No. Cases	Percentage, %
Synthetic cannabinoid cases	75	100
Male	68	91
Caucasian	23	31
Toxidrome		
– Sedative-hypnotic	9	12
– Sympathomimetic	7	9
– Serotonin syndrome	1	1
– Anticholinergic	1	1
Major vital sign abnormality		
– Tachycardia	12	16
– Bradycardia (HR < 50 bpm)	8	11
– Hypotension (SBP < 80 mm Hg)	2	3
– Hypertension (SBP > 200/or DBP >120 mm Hg)	2	3
– Bradypnea (RR < 10 breaths/min)	2	3
– Hyperthermia (T > 40.5°C [105°F])	1	1
CNS symptoms		
– Coma/CNS depression	22	29
– Agitation	18	24
– Delirium/toxic psychosis	16	21
– Seizures	11	15
– Hyperreflexia/myoclonus/clonus/tremor	7	9
– Hallucinations	4	5
Cardiac symptoms		
– Prolonged QRS (>120 ms)	1	1
– Prolonged QTC (>500 ms)	1	1
Pulmonary symptoms		
– Respiratory depression	6	8
– Aspiration pneumonitis	1	1
Acute kidney injury (Cr > 180 μmol/L [2 mg/dL])	5	7
Rhabdomyolysis (CPK > 1000 U/L)	4	5
Metabolic acidosis (pH < 7.2)	3	4
Hepatotoxicity (AST > 1000 U/L)	1	1
Deaths	0	0
Toxicological treatment		
– Benzodiazepines	26	35
– Antipsychotics	7	9
– Opioids	5	7
– Neuromuscular blockers	4	5
– Opioids	4	5
– Antihypertensives	2	3
Intravenous fluid resuscitation	23	31
Mechanical ventilation	9	12

HR indicates heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; RR, respiratory rate; T, temperature; Cr, creatinine; CPK, creatine phosphokinase; AST, aspartate transaminases.

toxicity.[1,2,5,6,8,11–13,21–24] A recent systemic review reported the adverse effects and treatment associated with synthetic cannabinoid use primarily in adults. The predominant users were young males (59%–100%). However, the most common manifestations were tachycardia, agitation, and nausea. Seizures occurred in 3.8% to 15%.[1] In contrast, Monte et al[13] reported on a predominance of CNS symptoms after synthetic cannabinoid exposure: agitation, delirium, and toxic psychosis in 41% of cases and seizures in 17% of cases. Their rates of treatment with benzodiazepine (37%) and antipsychotics (10%) were similar to ours (35% and 9%, respectively). Although admission to critical care units was similar between our study (25%) and Monte et al's[13] study (26%), a significant difference relates to the rate of intubation and mechanical ventilation. Twelve percent of our patients were mechanically ventilated compared with only 2% in Monte et al.[13]

Interestingly, the number of cases increased steadily each year reaching a maximum in 2015 (n = 27) with a sharp drop in 2016 (n = 7). Possible processes that may have contributed to this observation include the reclassification of synthetic cannabinoids as schedule 1 substances by the United States Drug Enforcement Agency in 2011, which over time would have decreased their availability. Second, the 2015 Monitoring the Future report showed an increasing perception of risk related to synthetic cannabinoid use among adolescents. Third, emergency care providers may be increasingly comfortable with managing synthetic cannabinoid exposures and, as a result, consulting medical toxicologists less frequently on such. Lastly, the decriminalization and legalization of marijuana in many states leading to its increasing availability and recently reported preferential use.[25–27]

Several study limitations merit emphasis. The ToxIC Case Registry was established in 2010 by the American College of Medical Toxicology as a prospective, nationwide, real-time surveillance tool. It exclusively captures cases that include bedside consultation by medical toxicology services; therefore, it is likely that novel and more serious exposures are overrepresented. Because medical toxicologists treating patients at the bedside collect all data, the clinical information obtained is highly reliable. Thus, the data captured in ToxIC complement that of the National Poisoning Data System maintained by United States Poison Control Centers, which receives phone calls from any source. Secondly, as most centers are located in academic tertiary care centers, ToxIC data may not necessarily reflect encounters in primary care settings. Lastly, by their nature, definitive chemical analysis and identification of specific synthetic cannabinoids are lacking in some cases. However, self-reporting has been shown as a reliable indicator of what the patient has been exposed to in substance abuse research.[28–30]

In summary, synthetic cannabinoid exposure should be taken seriously owing to the risk of critical illness associated with their use. Our study highlights the predominance of a wide variety of neuropsychiatric manifestations as well as wide spectrum of autonomic and other symptoms of synthetic cannabinoids in adolescents. Synthetic cannabinoids exposure does not typically present with a specific toxidrome and cannot be identified in routine hospital laboratory testing. Therefore, frontline providers should maintain a high index of suspicion and explore the possibility of synthetic cannabinoid exposure in adolescents presenting with unexplained altered level of consciousness or new-onset psychiatric symptoms.

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