Curr Psychiatry Rep (2016) 18: 52
DOI 10.1007/s11920-016-0694-1

Adverse Effects of Synthetic Cannabinoids: Management of Acute Toxicity and Withdrawal

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Published online: 14 April 2016

Abstract Although several chemical structural classes of synthetic cannabinoids (SCs) were recently classified as Schedule I substances, rates of use and cases of serious toxic effects remain high. While case reports and media bring attention to severe SC toxicity, daily SC use resulting in dependence and withdrawal is a significant concern that is often overlooked when discussing the risks of these drugs. There is a rich literature on evidence-based approaches to treating substance use disorders associated with most abused drugs, yet little has been published regarding how to best treat symptoms related to SC dependence given its recency as an emerging clinically significant issue. This review provides a background of the pharmacology of SCs, recent findings of adverse effects associated with both acute intoxication and withdrawal as a consequence of daily use, and treatment approaches that have been implemented to address these issues, with an emphasis on pharmacotherapies for managing detoxification. In order to determine prevalence of use in cannabis smokers, a population at high risk for SC use, we obtained data on demographics of SC users, frequency of use, and adverse effects over a 3.5-year period (2012–2015) in the New York City metropolitan area, a region with a recent history of high SC use. While controlled studies on the physiological and behavioral effects of SCs are lacking, it is clear that risks associated with using these drugs pertain not only to the unpredictable and severe nature of acute intoxication but also to the effects of long-term, chronic use. Recent reports in the literature parallel findings from our survey, indicating that there is a subset of people who use SCs daily. Although withdrawal has not been systematically characterized and effective treatments have yet to be elucidated, some symptom relief has been reported with benzodiazepines and the atypical antipsychotic, quetiapine. Given the continued use and abuse of SCs, empirical studies characterizing (1) SCs acute effects, (2) withdrawal upon cessation of use, and (3) effective treatment strategies for SC use disorder are urgently needed.

Keywords Spice · K2 · Synthetic cannabinoid · Adverse effects · Dependence · Withdrawal · Cannabis

Introduction

Use of synthetic cannabinoids (SCs) was first reported in Europe in the early 2000s and in the USA in 2008. The emerging popularity of SCs in the USA and severe risks associated with use became apparent when the number of SC intoxication calls to poison control centers increased by 240 % between 2010 and 2011 [1]. In an effort to curb sales and use of SCs, the Drug Enforcement Administration passed the Synthetic Drug Abuse Prevention Act in July 2012, which classified several chemical structural classes of cannabinoids as Schedule I substances [2], and was modified to include additional chemical classes and compounds in 2014 and 2015 [3–5]. As a consequence of this scheduling, new SC compounds have been developed to circumvent the bans; continued SC use and toxicity were evidenced by a 330 % increase in calls to poison control centers in 2015 from January to May [6]. During this time, severe adverse effects and deaths

This article is part of the Topical Collection on *Substance Use and Related Disorders*

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associated with SCs occurred at an alarming rate across the Midwest, Northeast, and Western regions of the country. For example, the Mississippi Poison Control Center (MPCC) received 721 suspected SC calls over a 1-month period (April–May); 11 % of the patients treated at the University of Mississippi Medical Center for suspected SC use were admitted to the general inpatient services, 10 % were admitted into intensive care services, and three patients died [7]. New York City was another region that experienced a rapid increase in SC-related toxicity cases. An advisory posted by the Department of Mental Health in April 2015 reported 120 SC-related emergency department (ED) visits in a single week, six times the average number of SC-related weekly visits until that point in 2015 [8]. Another advisory posted in September 2015 reported 2300 ED visits over July and August [9]. These statistics highlight the significant public health concerns regarding the use of SCs and the severity of acute toxicity. In light of the seriousness of the acute toxicity cases, reports on the apparently non-life-threatening adverse effects associated with daily use, including physiological dependence and withdrawal, are often overlooked. This review provides background on the preclinical pharmacology of SCs, highlights literature that has described the most common adverse effects associated with both acute toxicity and withdrawal from SCs, and summarizes treatment strategies for SC withdrawal and detoxification. In order to clarify current rates of SC use and effects associated with frequency of use, we also present survey data collected over 3.5 years from non-treatment seeking cannabis smokers in New York City, a population at high risk for SC use.

Preclinical Pharmacology

Over the last 40 years, hundreds of SCs have been synthesized to research the endocannabinoid system [10]. Similar to Δ^9-tetrahydrocannabinol (THC), the primary psychoactive component of cannabis, these compounds bind to the cannabinoid type-1 (CB1) and type-2 (CB2) receptors and produce their psychoactive and behavioral effects via CB1 receptor agonism [11, 12]. As with THC, prolonged exposure to SCs results in tolerance to agonist effects, decreased CB1 receptor expression and signaling in specific brain regions [13–17], and withdrawal symptoms upon cessation of drug administration (for review, see [18]). However, in vitro [19] and laboratory animal [20, 21, 22•] studies of the compounds identified in the first-generation SC products indicate that the pharmacodynamic and pharmacokinetic characteristics of SCs can differ considerably from THC by binding to the CB1 and CB2 receptors with higher affinity and efficacy. As such, these compounds elicit different behavioral- and physiological-effect profiles relative to THC [21, 23–25]. For instance, JWH-018, one of the first identified SCs, is significantly more efficacious, has higher CB1 affinity, and has a faster onset and shorter duration of action relative to THC [21, 24]. Additionally, active metabolites of JWH-018 and other SC compounds also bind to CB1 receptors with high affinity and efficacy [22•]. These pharmacodynamic and pharmacokinetic differences predict that SCs pose a greater risk for abuse and dependence than cannabis [26–29]. This has been demonstrated by the ability of SCs to maintain intravenous self-administration in rats, a preclinical model of abuse liability, whereas THC is not self-administered (for review, see [22•]). HU-210, another compound identified in SC products, is also more potent and efficacious than THC, yet its duration of action is nearly five times longer and its onset of action is significantly slower [30, 31]. While HU-210's slow onset and long duration of action do not necessarily predict greater abuse liability relative to cannabis, they do suggest that it is capable of producing protracted withdrawal symptoms analogous to what is observed with long-acting opioid agonists [32], predicting significant adverse effects associated with SC dependence and withdrawal. These findings highlight the pharmacological features of just a few out of the dozens of compounds that have been found in SC products that predict significant clinical physiological and behavioral risks relative to cannabis.

Synthetic Cannabinoids as Drugs of Abuse

Synthetic cannabinoids were initially developed for research purposes. As such, the methods for synthesizing the compounds are published in the scientific literature and utilized by clandestine chemists to produce compounds for commercial SC products [33]. Once synthesized, SCs are dissolved in ethanol or acetone and sprayed on plant material, which is then sold in packets as incense, herbal blends, or potpourri, and usually labeled with a disclaimer indicating that the contents are not for human consumption. These products are sold under a variety of names including "Spice," "K2," "Black Mamba," and "Scooby Snax." The chemical constituents and concentrations of compounds vary between and within packages [10, 34••]. Before these compounds were scheduled, they were marketed as a legal substitute to cannabis and used to avoid positive drug toxicology screens [35]. SCs are still readily available at retail shops and over the Internet despite their Schedule 1 status [4] with new compounds emerging with minor changes to the chemical structure made to circumvent DEA scheduling. The continuously changing composition of SC products makes treating SC toxicity particularly challenging because the individual compounds vary in potency, efficacy, and duration of action, making their effects unpredictable.

Case reports and retrospective studies of acute SC intoxication indicate that they can produce a wide range of physiological and psychiatric adverse effects, which vary in duration and severity [36••]. These reports describe the potential for

severe toxic effects of SC use including psychosis [37], respiratory depression [38], cardiac events including cardiac arrest [39, 40], nephrotoxicity [41], gastrointestinal problems including hyperemesis [42–45], severe rhabdomyolysis, hyperthermia [46], acute cerebral ischemia [47], and seizures [48]. The differences between cannabis and SC effects are likely due to the divergent pharmacological profiles of SCs and their metabolites relative to THC and its metabolites; many SCs and metabolites have higher CB1 receptor binding affinity and efficacy relative to THC, which predicts greater cannabinoid-receptor mediated effects in both the central and peripheral nervous systems [10]. Some SCs bind to non-cannabinoid receptors [33], which may, in part, contribute to the physiological and behavioral consequences reported in the literature. It is difficult to know the degree to which the effects observed are due solely to SCs since many patients present with preexisting psychiatric and medical conditions and other drug use which may enhance and predispose these patients to the negative effects of SCs. Additionally, because of the changing composition of SC products and lack of available toxicology screens, confirming use is frequently dependent upon patient self-report. Furthermore, many incidents involve patients who are using SCs daily (i.e., [49–51]). Because withdrawal symptoms in daily users are reported to occur as soon as 15 min after smoking [52], the extent to which adverse effects are due to acute intoxication or withdrawal is sometimes unknown.

There is a growing number of reports detailing adverse effects associated with withdrawal from daily SC use; patients report withdrawal symptoms as the primary reason for their continued use [53••]. Recently, 53 % of patients seeking treatment for SC use were recommended to receive inpatient care, while outpatient care was recommended for the other 47 %. The group requiring inpatient care was reported to be the third largest group of clients admitted to inpatient detoxification services in Auckland, New Zealand [53••]. As noted above, withdrawal has been reported to occur shortly after smoking, with one patient reporting that she would wake up every 45 min throughout the night to smoke in order to alleviate withdrawal symptoms [52]. Abrupt discontinuation of daily SC use has been associated with severe symptoms including reoccurring seizures and cardiovascular and respiratory risks (tachycardia, chest pain, palpitations, dyspnea). Common adverse effects of moderate severity include cravings, headache, severe anxiety, insomnia, nausea and vomiting, loss of appetite, and diaphoresis [52, 53••, 54–56]. Severity of withdrawal symptoms seems to correspond to amount of daily SC use. For instance, on average, patients treated for SC-related withdrawal requiring outpatient care reported smoking 4.6 g of SCs, whereas those requiring medically supervised detoxification on an inpatient unit reported smoking an average of 5.2 g per day; three patients requiring the most care in managing withdrawal symptoms smoked on average 8.5 g per day [53••]. As predicted by SC pharmacology, the more moderate withdrawal symptoms related to SC use are similar to those of cannabis withdrawal, including lack of appetite, irritability, and sleep disruptions [57]. However, the onset and severity of SC withdrawal symptoms reflect greater CB1 receptor efficacy and pharmacokinetic differences relative to THC. As such, managing and treating SC withdrawal poses a unique clinical challenge. These findings demonstrate that (1) there is a subset of SC users who seek treatment and (2) withdrawal symptoms range from mild requiring only outpatient care to severe warranting inpatient care and continuous monitoring.

Treatment for Intoxication and Detoxification

Adverse effects of intoxication have been reported to occur even in those who only used SCs once, whereas withdrawal from SCs has been reported to occur only in daily users. Symptom management for acute intoxication is frequently treated with supportive care and intravenous fluids to treat electrolyte and fluid disturbances [36••]. Many adverse effects associated with acute intoxication are identical to some withdrawal symptoms; consequently, they are treated similarly. Patients who present with irritability, agitation, anxiety, and seizures associated with intoxication [36••, 49] or withdrawal [52, 53••, 55] are generally administered benzodiazepines as a first-line treatment. Neuroleptics are also administered for acute psychosis and agitation [46, 58] and mania with psychotic symptoms [51]. Although not always effective, antiemetics have been administered for hyperemesis [36••, 44]. Table 1 highlights pharmacotherapies that have been implemented specifically for detoxification according to symptom. Quetiapine was effective in treating withdrawal symptoms in patients who failed to respond to benzodiazepines [53••, 55]. Naltrexone has been prescribed to one patient and appeared to reduce SC cravings associated with detoxification [52]. As highlighted in Table 1, some patients are polysubstance users and have co-occurring psychiatric disorders. As such, symptoms that appear to be related to SC withdrawal may in fact be due to underlying issues exacerbated by SC use and not necessarily a direct reflection of SC withdrawal. Nonetheless, withdrawal does occur in otherwise healthy patients. In fact, in one report, the three patients requiring the highest doses of quetiapine to alleviate withdrawal symptoms were otherwise healthy individuals with no psychiatric history [53••]. These patients were also heavy SC users suggesting, again, that magnitude of withdrawal may correspond to quantity of use.

Table 1 Pharmacotherapies for SC withdrawal

Number of patients	Withdrawal symptoms	Treatment	Treatment history and comorbidities	Other drug toxicology/ dependencies	History of use	Onset of symptoms
$n = 20$	Agitation ($n = 16$) Irritability ($n = 15$) Anxiety ($n = 10$) Mood swings ($n = 10$) Nausea and vomiting ($n = 8$) Loss of appetite ($n = 3$)	Diazepam (5–25 mg, daily) Quetiapine (25–400 mg, daily)	Schizophrenia ($n = 3$) Depression w/ psychosis ($n = 1$) Bipolar disorder ($n = 1$) Anxiety disorder ($n = 1$)	Nicotine dependence ($n = 5$) Alcohol dependence ($n = 2$)	Daily, 5.2 ± 3.4 g/day	1–2 h[a]
$n = 1$	Recurring seizures	Lorazepam Fosphenytoin (15 mg/kg)	History of depression and poly substance abuse	Amphetamine Methamphetamine Tramadol Diphenhydramine ETOH	Daily	>24 h[b]
$n = 1$	Anxiety, seizure prophylaxis Anxiety and depression General withdrawal symptoms Cramping Nausea Appetite stimulation Craving	Phenobarbital (100 mg, TID, tapered to 60 mg, TID, discontinued at discharge) Escitalopram (10 mg, increased to 20 mg at discharge) Clonidine (0.1 mg as needed) Tizanidine (8 mg as needed) Metoclopramide (10 mg as needed) Cyproheptadine (8 mg, QID) Naltrexone initiated on day 3 (25 mg; dose increase to 50 mg on day 7)	N/A	Cocaine	Daily, every 15–45 min	2 h[c]
$n = 1$	Severe anxiety, sweat and chills, cravings, headaches, insomnia, vivid dreams, weight loss, and sinus tachycardia	Lorazepam (2 mg, i.v.) Discharged with a short course of oral benzodiazepines	N/A	N/A	Daily for 1 year, 3 g/day	6 days[d]
$n = 1$	Chest pain, dyspnea, headache, diaphoresis, tremor anxiety, and sinus tachycardia	Low-dose benzodiazepines, hydroxyzine, and diphenhydramine (ineffective) Quetiapine (initial dose of 50 mg, with increase dose to maintain symptom relief; ineffective)	N/A	N/A	Daily for 8 months, 1–3 g/day	6 days[d]

Table 1 (continued)

Number of patients	Withdrawal symptoms	Treatment	Treatment history and comorbidities	Other drug toxicology/ dependencies	History of use	Onset of symptoms
$n = 1$	Internal unrest, craving, nightmares, profuse sweating, nausea, tremor, and headache Insomnia due to unrest and nervousness	Zopiclone (3.25–7.5 mg for 3 days, then discontinued; ineffective) Promethazine (25 mg; ineffective) Clonidine (0.175 mg; ineffective) Pramipexole (0.175 mg on day 11, increased to 0.35 mg on day 18; effective)	ADHD (untreated) Insomnia treated w/ zopiclone (7.5 mg) 4 days prior to admission	Negative for cannabinoids, benzodiazepines, amphetamine, cocaine, opiates, and methadone	Daily for 8 months, 1–3 g/day	1 day[e]

Onset of withdrawal symptoms as described by patients or the amount of time elapsing between a patient's last SC use and arrival to the ED

N/A information not provided

[a] [53••]

[b] [56]

[c] [52]

[d] [55]

[e] [54]

Synthetic Cannabinoid Use Among the Cannabis-Using Population

Prior to the US federal ban of 2012, studies probing the prevalence of SC use, reasons for use, and self-reported effects using online surveys and Internet searches among local and global populations [59–63] reported that SC use was highly prevalent in cannabis-using populations. Since DEA scheduling of several cannabinoids, SC use has continued to be a significant issue across the country. The New York metropolitan area has seen high rates of use with multiple health advisories posted by the New York City Department of Mental Health regarding SCs from 2014–2015. Though these advisories capture the severe risks associated with acute toxicity, we sought to determine the general demographics of SC users in the New York City metropolitan area and specifically among current cannabis users, a population at high risk for SC use.

Methods Over a 3.5-year period, from April 2012 to October 2015, which included federal scheduling of SCs, people responding to advertisements in local newspapers recruiting non-treatment seeking, healthy cannabis smokers for research studies at the New York State Psychiatric Institute were asked open-ended questions about their SC use. These confidential telephone interviews included questions regarding demographics (e.g., sex, age, race), current drug use, psychiatric and medical conditions, and current or past SC use. If participants reported using SCs, they were asked how often, if they liked the drug, and if they experienced any adverse effects of the drug. Participants who had not used SCs were asked if friends smoked SCs and possible reasons for their use. Those appearing eligible for participation in the cannabis research study based on the telephone interview were invited into the laboratory for further screening, which provided the opportunity to obtain more detail regarding SC use (i.e., precise frequency of use, adverse effects of SCs). All study procedures were approved by the Institutional Review Board of the New York State Psychiatric Institute and were in accord with the Declaration of Helsinki.

Data were coded according to personal use and friends use, frequency of use, quality of the high (like, neutral, dislike), and adverse effects of the drug. Frequency of SC use was categorized according to single use, occasional use (2–9 times), frequent use (10–50 times), heavy use (more than 50 times), and those who endorsed use but did not specify the number of occasions. For characterizing the adverse effects of the drug, the most common responses (n >10) were categorized and coded accordingly: headache, anxiety-like effects including paranoia and panic, vasovagal effects including feeling dizzy or fainting, gastrointestinal effects including vomiting or nausea, and cardiovascular and respiratory effects including "heart racing" and difficulty breathing. Those who

reported having friends who smoked the drug, but did not engage in personal use, were asked about their friends' reason for use. Data were coded according to most frequent responses, including availability, affordability, need for clean urine toxicology, in treatment for cannabis use or trying to quit smoking cannabis, curiosity, and/or liking of the drug. Differences in age and cannabis use (days per week and amount per day) between SC users and non-users were determined by unpaired *t* tests with Welch's correction. Differences between the two groups in sex were determined using Fisher's exact test and differences in race were determined using Chi-square test. Results were considered statistically significant when *p* values were equal to or less than 0.05. Statistical analyses were performed with Prism 6.0a for the Macintosh (GraphPad Software, Inc, 2012).

Results: Demographics Over the 3.5-year period, 1908 people (1358 men; 550 women) from the New York City metropolitan area responding to advertisements for cannabis-smoking research volunteers were asked about their SC use. Respondents averaged 33 ± 9 years of age; 32.3 % ($n = 617$) of callers reported using SCs at least once. As Table 2 portrays, the groups differed in age ($p < 0.001$); SC users were younger than non-users. The groups did not differ in sex, race, or current cannabis use.

Use Trends Over Time As depicted in Table 3, rates of self-reported history of SC use remained stable between April 2012 and September 2015. The percent of people reporting SC use over 6-month periods during this time ranged from 29 to 35 %, with the highest prevalence of self-reported history of use occurring between April 2013 and April 2014.

SC Users: Frequency of Use Of the 617 respondents who reported smoking SCs, 44.7 % ($n = 276$) reported only smoking one time, 32.5 % ($n = 201$) reported using occasionally (2–9 times), 6.6 % ($n = 41$) of respondents reported using frequently (10–50 times), 3.1 % ($n = 19$) of respondents reported heavy use (>50 times, ranging from 50–400 times), and 9.2 % ($n = 57$) did not specify frequency of use. Overall, only a small percentage [3.7 % ($n = 23$)] endorsed current or past SC with regularity ranging in duration (from 3 months to 2 years) and frequency (once per week to daily use). Of the respondents who reported frequent, heavy, and regular use ($n = 83$), 22.9 % ($n = 19$) specified current or a history of daily use.

Table 2 Demographic characteristics of SC users and non-users

	Users ($n = 617$)	Non-users ($n = 1291$)
Age (years)	31.2 ± 8.3*	34.2 ± 9.4
Race % (B/W/M)	56/11/33	65/9/26
Sex % (M/F)	73/27	70/30
Cannabis use		
Days/week	6.0 ± 1.6	6.0 ± 1.7
Cannabis cigarettes/day	10.0 ± 7.7	11.6 ± 9.2

Data are presented as means (±SD) or as percent population

B black, *W* white, *M* mixed/other, *M* male, *F* female

*$p \leq 0.0001$

Drug Liking and Effects The majority of users reported disliking SCs (56.4 %; $n = 348$), with 7.5 % ($n = 46$) reporting a strong dislike for the drug. A subset of respondents (15.4 %; $n = 95$) reported liking the drug, and 17.3 % ($n = 107$) provided a neutral response or no response. A small percentage of respondents reported that their subjective liking of the drug changed over time or that the drug effect was inconsistent causing them to like it sometimes and dislike it other times (3.4 %; $n = 21$). Overall, drug liking varied according to frequency of SCs use as portrayed in Table 4, with the majority of single-time users reporting disliking the SCs (70.3 %) whereas 52.6 % of daily users reported liking the drug.

The most common self-reported adverse effect of SCs among the 169 respondents was headache, reported by 30.2 % of the population ($n = 51$). Paranoia and panic were reported by 20.1 % of the population ($n = 34$), 10.1 % ($n = 17$) reported vasovagal effects including dizziness and fainting, cardiovascular and respiratory effects including "heart racing" and difficulty breathing was reported in 6.5 % ($n = 11$) of the population, and 8.2 % ($n = 14$) reported gastrointestinal effects including nausea and vomiting. As portrayed in Table 5, adverse effects varied according to frequency of use, with the single-time SC users constituting the largest proportion of each effect. Only 2 of the 19 daily users reported adverse effect (paranoia and headache). Severe effects including seizure ($n = 1$), respondents reporting that they felt like they were "dying" ($n = 9$), and difficulty breathing ($n = 4$) were reported by 5.9 % of the population; 66 % of these events occurred in people that had used SCs less than ten times. Four interviewees reported paralysis and loss of muscle tone.

Non-users Of the respondents who did not report having used SCs ($n = 1291$), 28.1 % ($n = 363$) reported having friends who used these drugs; 272 provided at least one reason for friends' cannabis use. The most frequent reason given for use was to substitute for cannabis so as to avoid positive urine toxicology tests ($n = 150$). Some specified that THC-negative urine toxicologies were required for probation or parole ($n = 73$), employment ($n = 11$), or for the military ($n = 2$). Other reasons given for use included low cost and availability ($n = 40$), liking or preference for SCs ($n = 38$), as a substitute for cannabis or trying to quit smoking cannabis ($n = 17$), out of curiosity ($n = 18$), or because it was legal ($n = 18$).

Table 3 Prevalence of self-reported SC use in cannabis-smoking research volunteers

	Reported use from 4/2012–9/2015						
	4/12–9/12	10/12–3/13	4/13–9/13	10/13–3/14	4/14–9/14	10/14–3/15	4/15–9/15
No use	68.0	70.9	65.2	65.0	68.9	67.1	70.6
Use	32.0	29.1	34.8	35.0	31.1	32.9	29.4

Self-reported history of SC use represented as percent of group interviewed according to the 6-month periods from April 2012 through September 2015

Discussion

SC use continues to be a significant public health concern despite repeated DEA scheduling of specific constituents of this class of compounds. Attention to the dangers of SCs has been largely due to the severe, life-threatening toxic effects described in case reports and highlighted in the media. In addition to these alarming adverse effects, the risks associated with daily SC use include dependence and withdrawal, a growing, often overlooked concern. The current survey findings demonstrate that SC use is highly prevalent among cannabis smokers, with a subset reporting daily use, and that many use SCs to avoid legal and professional ramifications associated with cannabis use. Even with strong public health and legislative efforts to decrease SC availability, reports of use have not changed over the last 3.5 years suggesting that this is a drug-use trend that is not declining. Those who smoked SCs more frequently reported liking the drug more with fewer adverse effects relative to the infrequent users; negative subjective reports and adverse effects were most prevalent among respondents who smoked SCs only once. This may indicate that people who smoke SCs regularly are a self-selecting group who has not experienced the negative effects of the drug or that tolerance may develop to the negative effects with repeated use. Similarly, a previous online survey of SC users, the majority of whom endorsed regular SC use (94 % of respondents), also reported positive subjective effects from the drug [60]. A subset of these participants reported inconsistencies across SC products, an effect that was also endorsed by the frequent and heavy SC users in the current study. The inconsistent effects are likely due to the several different cannabinoids and concentrations detected in a single product and across SC products [34••] and highlight the inherent and unpredictable risk of using these drugs.

While volunteers in the current study were not asked about withdrawal symptoms or their interest in treatment for their SC use, recent reports indicate that there is a population of daily SC users who seek treatment. These individuals experience withdrawal symptoms that occur soon after smoking, which vary in severity depending on amount and frequency of SC use [52, 53••, 54, 55]. Because this is a newly emerging issue, there has yet to be investigations into the most effective pharmacotherapies to treat SC use disorders; however, quetiapine appeared to be effective in managing withdrawal symptoms in some case reports [53••, 55]. Like THC, preclinical studies have demonstrated that SC withdrawal is mediated by the CB1 receptor, suggesting that pharmacotherapies for cannabis use disorders may be effective in treating SC withdrawal. Although there are currently no FDA-approved medications for cannabis use disorder, nabilone, a synthetic analogue of THC that is FDA-approved for

Table 4 Self-reported rating of SC high as a function of use

	Frequency of use					
	Single ($n=276$)	Occasional ($n=201$)	Frequent ($n=41$)	Heavy ($n=19$)	Regular ($n=23$)	Unknown ($n=57$)
Strong dislike	11.2	4.5	2.4	–	8.7	5.3
Dislike	70.2	55.7	41.5	21.0	13.0	31.6
Neutral/NA	12.7	18.9	14.6	5.3	26.1	36.7
Like	5.8	17.9	19.5	52.6	47.8	24.6
Change/inconsistent	–	3.0	22.0	21.1	4.3	1.8

Self-reported ratings of SC "high" are presented as percent of respondents using SCs once, occasionally (2–9 times), frequently (10–50 times), heavily (more than 50 times), those who did not specify frequency of use, and a subset of those who responded that they use regularly. A subset of participants reported that the effects were unreliable or changed over time indicated in the final row

Table 5 Adverse effects of SC high as a function of use

Frequency of use	Adverse effect				
	Headache ($n = 51$)	Panic ($n = 34$)	Vasovagal ($n = 17$)	GI effects ($n = 14$)	Cardio/resp ($n = 11$)
Single ($n = 85$)	27	11	11	8	4
Occasional ($n = 53$)	19	15	3	1	4
Frequent ($n = 11$)	2	–	2	2	
Heavy ($n = 3$)	1	1		–	–
Regular ($n = 7$)	–	5		1	2
Unknown ($n = 10$)	2	2	1	2	1

Effects of SCs reported with the greatest frequency among respondents (presented in parenthesis) who used SCs once, occasionally (2–9 times), frequently (10–50 times), heavily (more than 50 times), or those who did not specify frequency of use. Data presented are percent of the population endorsing a particular effect. Symptoms include headache, panic/paranoia, vasovagal reactions including dizziness and fainting, gastrointestinal upset including nausea and vomiting, and cardiovascular and respiratory effects

chemotherapy-induced nausea, has shown promise in laboratory studies of cannabis withdrawal and relapse. Nabilone has been shown to specifically alleviate cannabis withdrawal-associated disruptions in sleep, appetite suppression, and irritability [64], hallmark features of SC withdrawal, suggesting that nabilone may also be a potential pharmacotherapy for treating SC withdrawal.

The current findings demonstrate the prevalence of SC use, yet little is understood about the direct effects of these drugs in humans. Because these compounds were initially synthesized to further the understanding of cannabinoid drug-receptor signaling, there have been in vivo and in vitro studies of the pharmacokinetic and pharmacodynamic effects of these compounds. Preclinical laboratory studies have additionally contributed to the understanding of the behavioral effects and physiological risks associated with SCs relative to THC, data that are important to consider when predicting their behavioral activity in humans. However, with over 50 publications reporting cases of acute intoxication, and a small but growing number of reports on withdrawal symptoms after repeated SC use, the urgent need for human laboratory studies to evaluate both the acute effects of representative compounds with different pharmacodynamics and pharmacokinetic profiles (i.e., partial versus full agonists, short-acting versus long-acting compounds) and withdrawal under controlled conditions is clear. Comparing the effects of representative compounds will provide information that can be generalized to other compounds with similar pharmacological properties as they emerge onto the illicit drug market. Such studies are critical for providing the data necessary to inform and educate the public regarding the physiological and behavioral risks of these drugs and to help guide clinical care for SC abuse and dependence.

Conclusion

The current findings indicate that despite DEA scheduling, SC use continues to be a significant public health concern. The consequences of long-term, daily use are clearly emerging as a clinically significant issue, yet there is little guidance available for the treatment of problematic SC use and withdrawal. The continued popularity of SCs highlights the urgent need for controlled studies to characterize and develop effective treatment strategies for risks associated with both acute intoxication and chronic use.

Acknowledgments This research was supported by the US National Institute on Drug Abuse Grants DA039123, DA036809, and DA02775. The authors acknowledge and appreciate Dr. Margaret Haney for the discussion and feedback throughout manuscript preparation and the exceptional assistance of Damaris Rocha, Vivian Mao, Nicole Ann Borchard, Ursula Rogers, Olivia Derella, Bennett Wechsler, Stephanie Rivera, Chananda Thavisin, Divya Ramesh, and Jorge Ginory-Perez for interviewing participants and data collection.

Compliance with Ethical Standards All study procedures were approved by the Institutional Review Board of the New York State Psychiatric Institute and were in accord with the Declaration of Helsinki.

Conflict of Interest Ziva D. Cooper is a non-compensated board member of KannaLife, Inc. and has received consultancy fees from PharmaCann, LLC. Dr. Cooper has received research funds from Insys Therapeutics.

Human and Animal Rights and Informed Consent This manuscript does include data obtained from human subjects.

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