# Longitudinal Predictors of Synthetic Cannabinoid Use in Adolescents

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abstract

**BACKGROUND:** Synthetic cannabinoids (SCs) are a large, heterogeneous group of chemicals that are structurally similar to δ-9-tetrahydrocannabinol. Many SCs are high-efficacy full agonists of the CB1 and/or CB2 cannabinoid receptors, resulting in a potent group of chemicals with a variety of negative health effects, including death. SCs are available to adolescents at convenience stores and smoke shops and on the Internet. However, little is known about the risk factors that contribute to eventual use of SCs in adolescents, and no research has examined the psychiatric, personality, and substance-use risk factors that prospectively predict SC use. On the basis of extant cross-sectional research, we hypothesized that anxiety, depression, impulsivity, and marijuana use would prospectively predict eventual SC use.

**METHODS:** Data were collected across 2 time points 12 months apart on adolescents attending multiple public high schools in southeast Texas ($n$ = 964).

**RESULTS:** Path analysis indicated that depressive symptoms, marijuana use, alcohol use, and SC use at baseline were predictive of SC use at 1-year follow-up, whereas anxiety symptoms and impulsivity were not. In addition, SC use at baseline was not predictive of marijuana use at the 1-year follow-up. Females and African Americans were less likely to use SCs than males or those of other ethnicities.

**CONCLUSIONS:** SC-use prevention programming should consider depressive symptoms, marijuana use, and alcohol use as risk factors for SC use. Of particular significance, traditional marijuana use was predictive of subsequent SC use, but SC use was not predictive of later marijuana use.

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Mr Ninnemann conceptualized and designed the study and drafted the initial manuscript; Dr Jeong Choi conducted relevant statistical analyses and reviewed and revised the manuscript; Dr Stuart critically reviewed and revised the manuscript; Dr Temple coordinated and supervised data collection at all sites and critically reviewed the manuscript; and all authors 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:** Synthetic cannabinoids (SCs) are drugs that are similar to, but significantly stronger than, δ-9-tetrahydrocannabinol. Little is known about the toxicological profiles of SCs in humans. SCs are used by adolescents, often with negative effects that result in emergency department visits.

**WHAT THIS STUDY ADDS:** This study provides the first prospective examination of SC use, showing that depressive symptoms, marijuana use, and alcohol use are predictive of subsequent SC use in adolescents. Importantly, SC use does not predict later marijuana use.

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Synthetic cannabinoid receptor agonists (SCs) are a large, heterogeneous group of chemicals that are structurally similar to δ-9-tetrahydrocannabinol (THC) or that act on the same receptors as THC.[1] Such substances may be sprayed on a plant-based material that resembles cannabis and sold as "not for human consumption" potpourri or incense at convenience stores, head shops, and online retailers.[2] In addition, SCs are, at times, sold as a white powder. Many SCs are high-efficacy full agonists of the CB1 and/or CB2 cannabinoid receptors,[3] resulting in SCs that are often much more potent than THC. Indeed, research has shown that some SCs may be functionally as much as 40 to 660 times more potent than THC.[4] In addition, SCs do not contain cannabidiol, a major cannabinoid in the cannabis plant that possesses anxiolytic and antipsychotic properties.[5,6] It is thought that the potency of SCs combined with the lack of cannabidiol make SCs potentially psychosis-inducing.[4] Although a number of SCs have been outlawed to possess or sell in the United States,[7] SCs remain readily available and producers often replace recently outlawed SCs with novel SCs.

Recent reports have shown that SCs appeal to adolescents and young adults due to their perceived legality, affordable cost, attractive labeling, and their inability to be detected in urine drug screens.[4,8,9] Indeed, many adolescents involved with the criminal justice system (eg, probation) who are court-mandated to drug urinalysis report avoiding a positive drug test, which SCs successfully do on routine drug urinalysis panels, as a primary reason for use.[9] These findings are also seen among adult SC users, with 1 study finding that 71% of ever-SC users enrolled in drug treatment reported avoiding a positive drug test as a primary reason for use.[10] Clearly, drug urinalysis and criminal justice system involvement appear to be risk factors for SC use.

The prevalence of SC use among high school students in the United States has been assessed annually by the nationally representative Monitoring the Future (MTF) survey. Results show that SC use has declined from 8.8% and 11.3% among 10th and 12th graders, respectively, in 2012 to 4.3% and 5.2% among 10th and 12th graders, respectively, in 2015.[11] Thus, rates of SC use among high school students has steadily declined, which may be due, in part, to the outlawing of a number of known SC compounds, making accessibility to SCs more difficult. Even as rates of the reported use of SCs have declined, however, reports to poison control centers between 2013 and 2015 related to the use of SCs increased from 2668 to 7779,[12] representing an almost threefold increase in incidence over a 2-year period. Moreover, in the past year there has been a threefold increase in reports of deaths related to SC consumption in the United States, increasing from 5 deaths in January through May in 2014 to 15 deaths between January and May in 2015.[13] Furthermore, whereas overall rates of SC use have declined, research has shown that rates of SC use among routine marijuana users has decreased at a much slower rate than their nonusing and less-frequent marijuana-using peers.[14] Although there are a variety of SC compounds in existence with varying effect profiles, it is clear that SC use is often associated with a variety of deleterious consequences and that negative effects related to the consumption of SCs have increased substantially in the past year. With this in mind, a single SC-use episode has the potential to severely harm an adolescent.

Very little is known about the longitudinal predictors of SC use in adolescents. Prospective research on predictors of SC use is critical to inform intervention and prevention programming. To date, studies assessing SC use in adolescents have consisted of either cross-sectional designs[9,15–17] or case reports related to acute intoxication and/or the after effects of SCs,[8,18–24] with 1 study examining cohorts of adolescents across time.[14] Of these studies, 2 have examined the psychosocial correlates of SC use. Findings from these studies indicate that lifetime cigarette, marijuana, alcohol, and other illicit drug use robustly increased the odds of past-year SC use, with marijuana-use frequency being the strongest correlate of SC use.[15,17] Notably, studies to date do not assess whether marijuana use is predictive of SC use or vice versa. Given that marijuana is the most commonly used illicit drug by high school students in the United States,[11] it is important to delineate the temporal relations between these variables to inform adolescent substance-use and prevention efforts. To date, studies assessing the psychosocial correlates of SC use have not included mood and personality variables. To inform hypotheses regarding temporal relations, we drew from well-established individual difference risk factors for adolescent use of marijuana, a distinct but pharmacologically related substance. Depressive symptoms, anxiety symptoms, and impulsivity have been shown to be longitudinally linked to marijuana use in adolescents.[25,26] Thus, the current study prospectively assessed the temporal relations between impulsivity, depressive symptoms, anxiety symptoms, and other drug use with SC use and marijuana use in adolescents. We hypothesized that impulsivity, depressive symptoms, anxiety symptoms, alcohol use, and marijuana use at baseline would be predictive of SC use at 1-year follow-up.

## METHODS

### Procedures and Participants

Participants were adolescents who were enrolled in a longitudinal study examining adolescent risk behaviors.[27] Participants in the current study were high school students ($n$ = 964) recruited from 7 public schools in Texas (response rate: 62%) who were assessed twice, once during the spring of 2011 and once during the spring of 2012 (1-year interval). At baseline, participants had a mean age of 16.09 (SD = 0.79) years. The majority of participants were enrolled in the 10th (73%) or 11th (24%) grade at baseline, with ninth-graders (1%), 12th-graders (1%), and those who reported "other" (1%) comprising a much smaller portion of the sample. The sample was ethnically diverse: 31% African American, 29% white, 28% Hispanic, and 12% other. Fifty-six percent of participants were female. Before conducting the survey, parental permission and student assent were obtained. Self-reported pencil/paper surveys were administered during school hours across years. To increase the likelihood of honest reporting, school staff members were not present during the administration of the surveys and the students were informed that their answers were protected by a certificate of confidentiality. Students received $10 gift cards upon completing the baseline and follow-up surveys (retention rate: 92.7%). All study participants were approved by the last author's (J.R.T.) institutional review board.

### Measures

#### *SC Use and Marijuana Use (Baseline and Follow-up)*

SC use and marijuana use were queried by using items from the MTF survey, which annually collects nationally representative information on middle and high school students' substance-use patterns.[28] To assess past-year SC use, participants reported whether (yes = 1, no = 0) they used "synthetic marijuana (for example, Spice and K2)" in the past year. Participants also reported whether (yes = 1, no = 0) they used marijuana in the past year.

#### *Alcohol and Other Drug Use (Baseline)*

By using a yes/no response format, past-year alcohol use was assessed with the following question: "In the past year, did you use alcohol (more than just a few sips)?"[25] Past-year other drug use was assessed by the following question: "In the past year, did you use…?" Possible answers were (1) cocaine (powder, crack, or freebase), (2) inhalants (sniffed glue, huffing), (3) ecstasy (MDMA, X, XTC, E), and (4) amphetamines (speed, crystal, crank, ice). Notably, the "other drug use" category does not include nonmedical use of prescription medications such as Adderal (Teva Pharmaceuticals, North Wales, PA) or OxyContin (Purdue Pharma, Stamford, CT). Due to a relatively small endorsement of individual drugs in the "other drugs" category, participants were considered other drug users if they endorsed ≥1 of these drugs.

#### *Symptoms of Depression and Anxiety (Baseline)*

Depressive symptoms were measured by using 8 items from the Center for Epidemiologic Studies Short Depression Scale.[29] By using a 4-point scale anchored by 1 (<1 day) and 4 (5–7 days), participants reported their past-week depressive symptoms. Examples of items included "I felt depressed" and "My sleep was restless." To measure anxiety symptoms, 5 items were used from the Screen for Child Anxiety-Related Emotional Disorders.[28] By using a 3-point scale anchored by 1 (not true) and 3 (very true), participants responded to statements, such as "I am nervous" and "I worry about being as good as other kids." Reliability for depression and anxiety symptoms were acceptable at α = .80 and α = .85, respectively.

#### *Impulsivity (Baseline)*

Adapted from the Teen Conflict Survey,[30] impulsivity was measured with the following 4 items on a 5-point scale anchored by 1 (never) and 5 (always): "I have a hard time sitting still," "I start things but have a hard time finishing them," "I do things without thinking," and "I need to use a lot of self-control to keep out of trouble." We created an impulsivity composite variable on the basis of the mean score on 4 items. The internal consistency was acceptable, α = .74.

#### *Demographic Information*

Participants reported their sex, ethnicity, highest parental education (1 = did not graduate from high school, 2 = finished high school or received a general educational development, 3 = did some college or training after high school, or 4 = finished college), and age (1 = ≤12, 2 = 13, 3 = 14, 4 = 15, 5 = 16, 6 = 17, and 7 = 18 years or older). Because sex and ethnicity are categorical, we created dummy-coded variables for sex and ethnicity.

### Analysis

To explore whether internalizing symptoms, impulsivity, and different types of drug use (eg, alcohol, other drug, SCs, and marijuana) in the previous year predicted SC use and marijuana use over the following year, a path model with the weighted least-squares with mean- and variance- adjusted parameter estimates in Mplus 7.3 was used.[31] Mean- and variance- adjusted parameter estimates provide robust parameter estimates even when outcome variables are asymmetrically distributed.[32,33] We did not report model fit indexes because, by definition of a fully saturated model estimating all

possible associations, they are always perfect. We used a full information maximum likelihood method to handle missing data.[34] Because the individual data were nested in 7 schools, we created 6 school dummy variables to control for intraclass correlation (<0.04; both outcomes). All demographic information was included in the model as covariates.

## RESULTS

Table 1 shows applicable means, SDs, and frequencies for each variable. Table 2 presents raw numbers and percentages of marijuana (non) users and SC (non)users at baseline and follow-up. As shown in Table 3, female (adjusted odds ratio [aOR] = 0.60, $P = .005$) and African-American (aOR = 50, $P = .046$) adolescents were less likely to use SCs than were males and youth of other ethnicities. In addition, symptoms of depression were positively related to SC use at 1-year follow-up (aOR = 1. 42, $P = .04$). Moreover, alcohol (aOR = 1.85, $P = .02$), marijuana (aOR = 2.47, $P < .001$), and SC (aOR = 2.36, $P < .001$) use at baseline were positively related to SC use in the following year. In addition, alcohol (aOR = 1.96, $P < .001$) and marijuana (aOR = 4.52, $P < .001$) use at baseline were positively related to marijuana use at the 1-year follow-up. Anxiety symptoms, impulsivity, other drug use, and SC use measured at baseline as well as all demographic variables were not significantly related to marijuana use at the 1-year follow-up.

**TABLE 1** Key Variables

| Variables | Values |
|---|---|
| Past-year substance use, *n* (%) | |
| SCs, baseline (*n* = 955) | |
| No | 831 (87.29) |
| Yes | 124 (12.98) |
| SCs, follow-up (*n* = 889) | |
| No | 776 (87.29) |
| Yes | 113 (12.71) |
| Marijuana, baseline (*n* = 958) | |
| No | 664 (69.31) |
| Yes | 294 (30.69) |
| Marijuana, follow-up (*n* = 889) | |
| No | 548 (61.64) |
| Yes | 341 (38.36) |
| Alcohol, baseline (*n* = 959) | |
| No | 408 (42.54) |
| Yes | 551 (57.46) |
| Other drugs, baseline (*n* = 957) | |
| No | 880 (91.95) |
| Yes | 77 (8.05) |
| Baseline mental health, mean ± SD | |
| Depression symptoms (*n* = 964; range:1–4) | 1.84 ± 0.59 |
| Anxiety symptoms (*n* = 964; range: 1–3) | 1.92 ± 0.49 |
| Impulsivity (*n* = 963, range: 1–5) | 2.35 ± 0.86 |

Sample sizes for each variable may be different due to missing data.

## DISCUSSION

In the first longitudinal study to examine SC use, we found that depressive symptoms, alcohol use, marijuana use, and SC use measured at baseline temporally predicted SC use 1 year later. These results corroborate previous cross-sectional studies showing significant correlations between alcohol, marijuana, and SCs. Importantly, however, our findings extend this work, showing that marijuana use and alcohol use introduce an increased risk of later SC use in adolescents. In contrast, after controlling for demographic characteristics, other variables, and baseline marijuana and alcohol use, SC use at baseline did not increase the risk of marijuana use over time, suggesting that marijuana may increase the risk of SC use, but not vice versa. With respect to mental health, we found that depressive symptoms, but not anxiety or impulsivity, were predictive of later SC use, suggesting that symptoms of depression may increase the likelihood of adolescents using SC. Given the lack of cannabidiol in SCs, which are known to provide anxiolytic effects, it may not be surprising that those with anxiety symptoms were not at increased risk of SC use, because SCs may more easily induce anxiety than marijuana. We also found that,

**TABLE 2** Frequency of Marijuana and SC Users and Nonusers at Baseline and at Follow-up

| | | Follow-up, *n* (%) | | | |
|---|---|---|---|---|---|
| | Baseline, *n* (%) | No Marijuana or SC Use | Marijuana Use Only | SC Use Only | Both Marijuana and SC Use |
| No marijuana or SC use | 596 (69) | 479 (80) | 99 (17) | 4 (1) | 14 (2) |
| Marijuana use only | 156 (18) | 27 (17) | 98 (63) | 1 (1) | 30 (19) |
| SC use only | 7 (1) | 4 (57) | 1 (14) | 0 (0) | 2 (29) |
| Both marijuana and SC use | 104 (12) | 17 (16) | 26 (25) | 1 (1) | 60 (58) |

**TABLE 3** Temporal Relationship Between SC Use, Marijuana Use, and Independent Variables

| | SC Use (Follow-up) | | | Marijuana Use (Follow-up) | | |
|---|---|---|---|---|---|---|
| | Estimation | SE | Odds Ratio | Estimation | SE | Odds Ratio |
| Female (= 1) versus male (= 0) | −0.51** | 0.18 | 0.60** | −0.21 | 0.12 | 0.81 |
| Hispanic (= 1) versus others (= 0) | −0.11 | 0.29 | 0.90 | −0.38 | 0.19 | 0.69 |
| White (= 1) versus others (= 0) | 0.32 | 0.29 | 1.38 | −0.17 | 0.20 | 0.85 |
| Black (= 1) versus others (= 0) | −0.69* | 0.35 | 0.50* | −0.01 | 0.20 | 0.99 |
| Age | −0.03 | 0.12 | 0.97 | −0.05 | 0.08 | 0.95 |
| Highest parental education | 0.01 | 0.09 | 1.01 | −0.07 | 0.05 | 0.93 |
| Depression symptoms | 0.35* | 0.17 | 1.42* | −0.08 | 0.12 | 0.92 |
| Anxiety symptoms | −0.16 | 0.21 | 0.85 | 0.04 | 0.15 | 1.04 |
| Impulsivity | 0.03 | 0.10 | 1.03 | −0.02 | 0.08 | 0.98 |
| Other drug use (baseline) | 0.35 | 0.25 | 1.42 | 0.14 | 0.22 | 1.15 |
| Marijuana use (baseline) | 0.90*** | 0.19 | 2.47*** | 1.51*** | 0.14 | 4.52*** |
| Alcohol use (baseline) | 0.62* | 0.27 | 1.85* | 0.68*** | 0.13 | 1.96*** |
| SC use (baseline) | 0.86*** | 0.20 | 2.36*** | 0.24 | 0.21 | 1.27 |

Schools were included in the model as dummy variables but are not presented here.

* $P < .05$,

** $P < .01$,

*** $P < .001$.

although depressive symptoms were predictive of SC use over time, this same relationship did not emerge with respect to marijuana use. Female and African-American adolescents were less likely to use SCs than were males and white and Hispanic adolescents, which is consistent with Palamar and Acosta's[17] findings in a nationally representative sample of adolescents.

In addition, we found that ∼13% of adolescents reported the use of SCs in the past year at baseline. This finding represents a prevalence of adolescent SC use that is notably higher than the most recent results from the nationally representative MTF survey, collected in 2015, which found that 4.3% and 5.2% of 10th- and 12th-graders, respectively, reported using SCs in the past year.[11] Importantly, our data were collected during the spring of 2011. MTF prevalence rates of SC use from 2012, the first year that SC use was queried, show that 11.3% of 12th-graders reported past-year use. In this way, our sample's rates of SC use are not dissimilar from nationally representative rates collected around the same time.

Study limitations include the prospective nature of the design with a regional sample despite diverse ethnicities, which precludes causal conclusions about the relationship between variables. In addition, third variables (eg, nonmedical prescription drug use) not included in this study could influence the reviewed relationships. Substance use was also measured by using a dichotomized yes/no variable. Furthermore, it is possible that the relations between variables could be bidirectional. Future research should incorporate more-thorough assessments including measures of substance-use frequency and substance-use problems and investigate the bidirectionality of these relations. In addition, future researchers should consider recruiting students in early middle school, before the onset of substance use and some mental health problems.

The substantial risks associated with even a single episode of SC use emphasize the critical importance of identifying and targeting potential risk factors. Our findings indicate that prevention and intervention efforts may benefit from targeting depressive symptoms and alcohol and marijuana use to potentially reduce adolescent use of SCs. Given our findings that marijuana is temporally predictive of SC use, but not vice versa, and in conjunction with recent research showing slower declines in use among younger[14] frequent marijuana users compared with their peers, prevention programming for SC use may be wise to take a tailored approach focusing specifically on reducing the risk of use among marijuana users as well as those involved in the criminal justice system. Notably, little is known regarding drug expectancies or the expectations one has about what will result from engagement in SC use. Given the promise of expectancy paradigm challenges to reduce alcohol use among adolescents,[35] understanding expectancies for SC use for adolescents may yield similar promise for prevention programming.

**ABBREVIATIONS**

aOR: adjusted odds ratio
MTF: Monitoring the Future
SC: synthetic cannabinoid
THC: δ-9-tetrahydrocannabinol

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