ORIGINAL ARTICLE

Consumption of Synthetic Cannabinoids in Adult Attention-Deficit/Hyperactivity Disorder: a Pilot Study

Alexandra P. Lam, et al. *[full author details at the end of the article]*

Abstract

Attention-deficit/hyperactivity disorder (ADHD) is associated with an increased risk for substance abuse and addiction. Synthetic cannabinoids (SC) have gained rising importance as their consumption increased rapidly in the last few years. However, SC consumption in patients with adult ADHD has not been investigated yet. A prospective clinical pilot study was conducted, including 60 adults with ADHD, assessing the prevalence of SC consumption and its associations with psychiatric comorbidities and patient characteristics. A drug consumption survey was utilized to investigate the use of SC and other drugs. Current ADHD symptoms were evaluated via ADHD Self-Rating Scale (ADHD-SR) and retrospective childhood ADHD symptom severity via Wender Utah Rating Scale (WURS-k) questionnaire. A positive lifetime prevalence of SC consumption was found in 15.0% of the analyzed sample. SC consumption was significantly associated with current smoking, lifetime use of natural cannabis (NC), cocaine, amphetamines, and benzodiazepines. Lifetime NC consumption was indicated by 65.0% and found to antecede SC use in adult ADHD patients. Logistic regression analysis identified substance use disorder and male sex as predictive for SC consumption. Patients with history of SC use scored significantly higher in both WURS-k and ADHD-SR questionnaire compared with nonusers and suffered significantly more frequently from psychiatric comorbidities. Main side-effects of SC included gastrointestinal, cardiovascular, and neuropsychiatric symptoms. SC consumption in adults with ADHD is frequent and associated with stronger ADHD symptom severity. Given the underestimated dangerous effects and related comorbidities, SC use should be subject to scrutiny by clinicians treating ADHD patients. More studies are needed to further elucidate the impact of SC use in ADHD.

Keywords Synthetic cannabinoids (SC) · Spice · New psychoactive substances (NPS) · Substance use disorder (SUD) · Attention deficit hyperactivity disorder (ADHD) · Adult ADHD

In the last few years, the consumption of new psychoactive substances (NPS), also known as "legal highs" or "smart drugs," has increased in Europe and the United States (Duffert 2014; Law et al. 2015; Muller et al. 2016). Synthetic cannabinoids (SC) are the largest group of NPS

Alexandra Philipsen and Helge H. O. Müller are equal contributors.

and have been developed to imitate the effects of (–)-trans-Δ9-tetrahydrocannabinol (THC), which displays the principal psychoactive constituent of natural cannabis (NC), by showing binding affinity to cannabinoid receptors (Miliano et al. 2016). Yet, the affinity, efficacy, and potency of SC for cannabinoid receptors are higher compared with THC (Miliano et al. 2016). While the impact of THC on mental disorders have been intensively investigated in previous studies (Lowe et al. 2019), data on SC consumption among psychiatric patients are scant (Bassir Nia et al. 2016; Welter et al. 2017). Attention-deficit/hyperactivity disorder (ADHD) is a frequent psychiatric disorder (Fayyad et al. 2017) with high individual, sociodemographic, and economical relevance (Fayyad et al. 2007; Leibson et al. 2001). One of the reasons for substantial medical costs of ADHD are comorbidities, as around 80% of adults with ADHD also suffer from at least one comorbid psychiatric disease (Katzman et al. 2017; Libutzki et al. 2019). The most common co-occurring psychiatric comorbidities comprise depression, bipolar disorder, anxiety disorders, personality disorders, e.g., Borderline Personality Disorder (BPD), and substance use disorders (SUDs) (Katzman et al. 2017). A notable prevalence of 15–50% of adults and adolescents with ADHD have been found affected by SUD (Wilens et al. 2018). On the contrary, a prevalence of 25–40% of adolescents and adults with SUD has been found also having ADHD (Wilens et al. 2018). ADHD and SUD comorbidity occurs at a very young age and shows a faster transition from less to more severe (Fatseas et al. 2016). Moreover, ADHD patients with SUD are at a very high risk to suffer from further psychiatric comorbidities, especially BPD, bipolar disorder, anxiety disorders, and posttraumatic stress disorder (PTSD) (Crunelle et al. 2018; van Emmerik-van Oortmerssen et al. 2014). It is also well known that SUD patients with ADHD suffer from more complex, chronic as well as more poly-substance use than SUD patients without ADHD (Crunelle et al. 2018). Moreover, ADHD patients are especially known to experiment with licit and illicit substances (Estevez et al. 2016). However, no available study has investigated the epidemiology of SC consumption in an ADHD population yet.

SC are known to cause various dangerous side effects and to show unpredictable toxicity, poisoning as well as lethal consequences (Mills et al. 2015; Muller et al. 2016). Most of the reported acute side effects include neuropsychiatric manifestations and sympathomimetic-cardiac effects (Bulbena-Cabre et al. 2018; Mills et al. 2015; Moeller et al. 2017; Muller et al. 2016; Spaderna et al. 2013). Among others, severe hallucinations, psychosis, anxiety, suicidality, self-harm, and physical side effects, such as strokes or heart attacks, have been observed in previous studies (Muller et al. 2016). Additionally, SC are known to cause euphoria, anti-nociception, concentration problems, changed perception, and acute memory impairment (Kaló et al. 2018; Nurmedov et al. 2015). Hospitalizations and deaths related to SC have also been reported (Duffert 2014; Kemp et al. 2016; Miliano et al. 2016; Nichols 2011). However, users are often unaware of the potentially harmful consequences, as SC are marketed as legal and safe replacements for NC (Miliano et al. 2016). SC are sold as herbal smoking mixtures, plant materials, extracts, tablets, or powders (Kapka-Skrzypczak et al. 2011; Schmidt et al. 2011) and have appealing names like "spice," "spice gold," "diamond-spice," "K2," "legal or synthetic marijuana," "black mamba," "crazy clown," and many more (Law et al. 2015; Muller et al. 2016). Additionally, SC are relatively inexpensive, easy to purchase, and their consumption can only be detected in specialized laboratories (Duffert 2014; Kemp et al. 2016; Miliano et al. 2016; Mills et al. 2015; Spaderna et al. 2013). As manufacturers keep on rapidly developing new SC compounds with marginally modified chemical structures (Kapka-Skrzypczak et al. 2011; Miliano et al. 2016), new SC products are sold until they are identified and banned by law (Fattore and Fratta 2011).

A recent fMRI study examining the influence of ADHD on network topology alteration in adolescent SC users emphasizes the further need of investigating SC use among ADHD patients (Çelik et al. 2019). ADHD is regarded as a significant risk factor for substance use, abuse, and dependence (Crunelle et al. 2018; Soler Artigas et al. 2019). Above all, natural cannabis (NC) is reported as the most commonly used illicit drug among patients with ADHD (Soler Artigas et al. 2019). The dopaminergic neurotransmission pathway is crucially associated with ADHD and previous studies even revealed similar deficits in dopamine transmission in ADHD and SUD (Luo and Levin 2017). NC and SC show dopamine receptor interactions and induce dopamine release in several brain areas, but SC have been found showing even higher potency in releasing dopamine (Miliano et al. 2016).

In this prospective clinical pilot study, the prevalence of SC consumption in lifetime history of ADHD patients was investigated. Given the high novelty-seeking behavior in ADHD patients (Donfrancesco et al. 2015), their susceptibility of experimenting with illicit substances (Estevez et al. 2016), and their high risk of substance abuse (Soler Artigas et al. 2019), we hypothesized a high rate of SC consumption among ADHD patients. The prevalence found in our ADHD sample was then compared with previously published data. Moreover, effects and side effects induced by SC among ADHD patients were evaluated. Also, the prevalence of NC use was assessed and a comparison of consumer profiles as well as symptom severity between user and nonuser of both groups performed. In addition, as ADHD is often associated with several comorbid psychiatric diseases, especially the impact of psychiatric comorbidities on SC or NC use was analyzed.

Methods

Study Design, Setting, and Participant Recruitment

A clinical-based study was conducted with adult ADHD patients consecutively recruited from the inpatient and outpatient clinics of the University Hospital of Psychiatry and Psychotherapy at the Carl-von-Ossietzky University of Oldenburg in Germany between June 2017 and December 2017. All ADHD patients above 18 years of age were included in the study, without further exclusion criteria applied. The diagnosis of ADHD was established by psychiatric expert assessment. ADHD patients had to fulfill the criteria for ADHD according to DSM-IV based on international guidelines. To verify the diagnosis, diagnostic interviews as well as self-rating scales were utilized.

In total, 62 patients participated in the study. Two patients were excluded from data analysis due to unreadable questionnaires. Thus, the study sample comprised 60 patients with ADHD. Eight patients (13.3%) were recruited from inpatient and 52 (86.7%) from outpatient units.

Instruments

Current ADHD symptom severity was assessed via the self-rating instrument ADHD Self-Rating Scale (ADHD-SR, German Version (Rosler et al. 2004)). For the retrospective assessment of ADHD symptom severity in childhood, the self-rating questionnaire Wender Utah Rating Scale (WURS-k (Retz-Junginger et al. 2003)) was used. To assess axis I and axis II disorders, the structured clinical interview for DSM-IV was utilized (SCID-I, SCID-II (Wittchen et al. 1997)). Sociodemographic data, medical history, and history of drug consumption were assessed via questionnaire and drug consumption survey.

Statistical Analysis

Statistical analyses were conducted with SPSS Version 25. A descriptive analysis was performed for all variables included in further analyses. Frequencies are reported for categorical variables. For metric variables the mean and standard deviation were calculated. Since the study is based on a clinical population, normal distribution could not be assumed for most of the variables. In these cases, non-parametric statistics were used. SC prevalence will be descriptively compared with previously published data. Association of SC or NC consumption and experiences with smoking, alcohol, cocaine, NC, heroine, amphetamines, and benzodiazepines were tested via Spearman correlations.

Logistic regression models were constructed with NC or SC as response using backward stepwise elimination. The following variables were considered in stepwise regressions and entered into the analyses if a significant influence could be found: age (in years), sex (reference category (RC) female), ADHD medication (RC no), SUD (RC no), affective disorder (RC no), anxiety disorder (RC no), obsessive compulsive disorder (OCD) and somatoform disorders (RC no), posttraumatic stress disorder (RC no), BPD (RC no), axis II disorders other than BPD (RC no), autism (RC no), graduation (RC low), living in a partnership (RC no), and somatic medication (RC no).

Separate chi-square tests were used to assess the relationship between SC use and sociodemographic characteristics (civil status, living in a partnership, professional status, and employment rate or inpatient psychiatric treatment). The prevalence of sociodemographic and medical characteristics in the SC versus NC-only subgroup were also compared by using separate chi-square tests.

To determine whether SC users or NC users differ from nonusers with regard to severity of current and retrospective childhood ADHD symptoms, a two-sided t test was performed after testing for normal distribution using the Shapiro-Wilk test. p values were 2-tailed and considered significant if less than .05.

Results

Participant Characteristics

The age of the study sample ranged from 18 to 55 years with a mean age of $M = 30.72$ ($SD = 9.34$). The majority of participants were male. Nineteen patients received psychopharmacological ADHD treatment. Of these, fifteen were treated with the stimulant medication methylphenidate, as the recommended first-line treatment for ADHD (Kooij et al. 2010). Four patients took the non-stimulant medication atomoxetine (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften 2017). More than half of our participants suffered from at least one comorbid psychiatric disease, most commonly affective disorder and SUD. Further sample characteristics and histories of substance use are summarized in Tables 1 and 2.

SC Consumption Prevalence and General Drug Experience of the Sample

Of all study participants, 15.0% reported a history of SC consumption. The majority of participants (66.7%) indicated lifetime experiences with illicit drugs. The most frequently consumed drug was NC, followed by amphetamine, cocaine, SC, benzodiazepines, and heroine (see Table 2). Three

Table 1 Characteristics of the study sample (total sample, $N = 60$)

		Number	Percentage
Sex	Female	17	28.3
	Male	43	71.7
Civil status	Unmarried	41	68.3
	Married	10	16.7
	Separated	2	3.3
	Divorced	4	6.7
	Widowed	0	0.0
Graduation	No graduation	3	5.0
	Secondary schools (5–9)	19	31.7
	Secondary schools (5–10)	17	28.3
	General qualification for university entrance	19	31.7
Professional status	Unemployed	16	26.7
	Student	8	13.3
	Employee	29	48.3
	Pensioner	1	1.7
	Self-employed	2	3.3
	Other	1	1.7
Physical illness	No	26	43.3
	Yes	20	33.3
Medication intake	No	19	31.7
	Yes	29	48.3
Antidepressants	No	49	81.7
	Yes	10	16.7
Neuroleptics	No	56	93.3
	Yes	3	5.0
Somatic medication	No	49	81.7
	Yes	10	16.7
ADHD medication	No	42	70.0
	Yes	19	31.7

ADHD, attention-deficit/hyperactivity disorder

patients indicated experiences with other rarely used substances, such as LSD, mushrooms, thorn apple, psilocybin, and *Salvia divinorum*. In terms of alcohol, most participants reported an at least occasional consumption. More than every second study participant was a smoker.

(Side) Effects Associated with SC Use

All SC users reported more or less uncomfortable (side) effects , with high variability, after intake of SC. The most frequently mentioned effects were decreased motor coordination, dizziness, and nausea. One male indicated feeling nauseated, dizzy, and extremely tired after SC intake and rated these effects as very severe at a relatively low dose of approximately 0.1 g. Another female described feelings of euphoria, nausea, emesis, and dizziness after SC consumption as pills without enjoying the stated effects. Yet, this female participant reported a co-use of other psychotropic medications, speed, cannabis, and alcohol. Another 35-year old male, the oldest of all SC users mentioned experiencing erectile dysfunction after SC use, and indicated that SC led to more intense, inconvenient side effects than NC. The intake of SC was reported to be excitatory and sexually exciting but was accompanied with impotence (see Fig. 1 for further detail). None of the study participants revealed the desire or the intention to consume SC in the future.

Table 2 Characteristics of the study sample: comorbid psychiatric disorders and history of substance use

		Number	Percentage
Smoker	No	26	43.3
	Yes	34	56.7
At least one psychiatric comorbidity	No	23	35.4
	Yes	37	56.9
Affective disorder†	No	32	53.3
	Yes	28	46.7
Anxiety disorder†	No	54	90.0
	Yes	6	10.0
OCD, somatoform disorder†	No	58	96.7
	Yes	2	3.3
PTSD†	No	55	91.7
	Yes	5	8.3
Axis II disorders†	No	54	90.0
	Yes	6	10.0
Autism†	No	59	98.3
	Yes	1	1.7
SUD†	No	50	83.3
	Yes	10	16.7
Lifetime consumption of SC	No	51	85.0
	Yes	9	15.0
Alcohol consumption	No	16	26.7
	Yes	44	73.3
	Occasional (every few month)	24	36.9
	More than twice a month	14	21.5
	More than once a week	5	7.7
	Daily	1	1.5
Experience with other illicit drugs than SC	No	20	33.3
	Yes	40	66.7
NC†	No	21	35.0
	Yes	39	65.0
Cocaine†	No	46	76.7
	Yes	14	23.3
Heroine†	No	56	93.3
	Yes	2	3.3
Amphetamine†	No	45	75.0
	Yes	15	25.0
Benzodiazepines†	No	57	95.0
	Yes	3	5.0
Others†	No	55	92.3
	Yes	5	7.7

OCD obsessive compulsive disorder, *SUD* substance use disorder, *PTSD* posttraumatic stress disorder, *SC* synthetic cannabinoids, *NC* natural cannabis

†Multiple categories can apply

SC Consumer Characteristics

All SC users were smokers with history of NC consumption. Furthermore, all SC users suffered from comorbid psychiatric disorders, with a high rate of comorbid SUD (55.6%) compared with non-SC users (9.8%). Moreover, all SC users were undergoing outpatient psychiatric treatment (77.8%) due to a comorbid moderate or severe depressive disorder.

In the SC subgroup the average age of first NC consumption was significantly lower ($M = $ 15.44 years, $SD = 1.667$, range 13–18) than the average age of first SC consumption (see
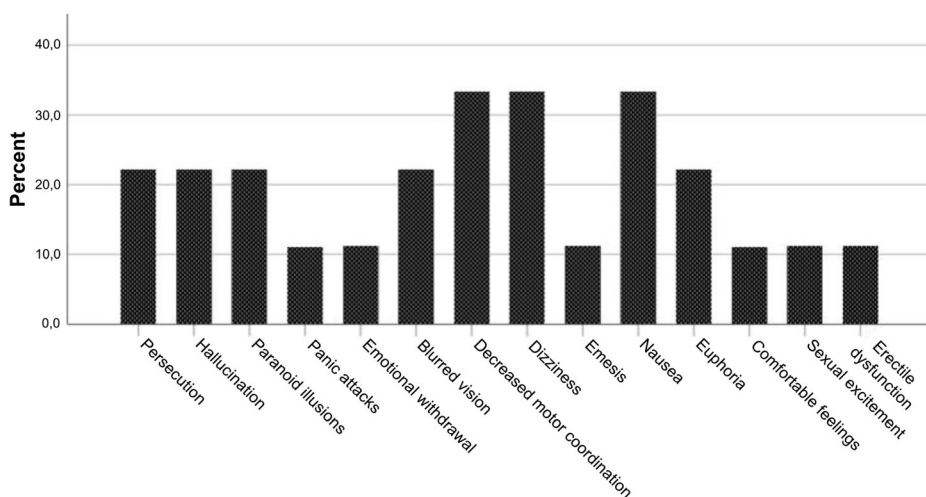
Fig. 1 Proportion of reported (side) effects associated with SC use (across subjects). SC, synthetic cannabinoids

Table 3) (t (39) = 25.065, $p < .001$). The majority (67.0%) indicated having consumed SC only once, whereas 22.2% indicated history of regular SC consumption more than twice a month. The substances were mostly bought on the internet (44.4%), through acquaintances (44.4%), in tobacco stores (22.2%), or at headshops (11.1%). No significant relationship could be found neither for SC use and civil status, living in a partnership, professional status, employment rate, nor inpatient psychiatric treatment (data not shown). Further detailed information about the consumer profiles of SC users are depicted in Table 3.

NC Consumption Prevalence and Consumer Characteristics

NC consumption experience was the most frequently consumed illicit drug, indicated by $n = 39$ (65%) of the participants. Most NC consumers ($n = 29$, 74.4%) were male, and the majority ($n = 28$, 71.8%) suffered from at least one comorbid psychiatric disorder. As all SC users revealed history of NC consumption, subgroup analyses of NC users without SC experience (NC-only) were performed.

NC-Only Consumer Characteristics

Characteristic of NC-only users are depicted in Table 3.

Comparison of SC and NC-Only Users

Chi-square tests comparing the prevalence rates of sample characteristics between SC users and NC-only users revealed that ADHD patients with history of SC use suffered significantly more frequently from at least one comorbid psychiatric disorder, compared with patients with history of NC-only use (see Table 3). Comorbid substance use disorder was 3 times higher among ADHD patients with SC use than among patients with NC-only lifetime experience,

Table 3 Characteristics of the study sample (SC versus NC-only users)

	SC (*n* = 9)		NC-only (*n* = 30)				
Age, years							
M (SD)	28.44 (6.41)		32.43 (9.58)				
Range	18–38		18–55				
Gender, % (n)							
Male	88.9 (8)		73.3 (22)				
Female	11.1 (1)		26.7 (8)				
Age of first consumption, years							
M (SD)	20.88 (7.10)		16.08 (3.51)				
Range	14–35		12–32				
	n	%	*n*	%	χ²	df	p
Smoker	9	100.0	20	66.7	4.03	1	*0.045**
Current ADHD medication	1	11.1	7	17.95	0.63	1	0.426
At least one psychiatric comorbidity	9	100.0	19	66.7	4.60	1	*0.032**
Affective disorder†	6	66.7	13	43.3	1.88	1	0.171
Anxiety disorder†	1	11.1	4	13.3	0.03	1	0.861
OCD, somatoform disorder†	0	0.0	2	6.7	0.63	1	0.426
PTSD†	2	22.2	2	6.7	1.82	1	0.177
Axis II disorders†	2	22.2	4	13.3	0.42	1	0.517
BPD†	2	22.2	3	10.0	0.93	1	0.336
Autism†	0	0.0	0	0.0	–	–	–
SUD†	5	55.6	4	13.3	6.95	1	*0.008**
Alcohol consumption							
None	3	33.3	6	20.0	0.69	1	0.405
Occasional (every few month)	3	33.3	10	33.3	0	1	1.000
More than twice a month	3	33.3	11	36.7	0.03	1	0.854
More than once a week	2	22.2	2	6.7	1.82	1	0.177
Daily	0	0.0	4	13.3	1.34	1	0.248
Experience with other drugs than SC	9	100.0	30	100.0	–	–	–
NC	9	100.0	30	100.0	–	–	–
Cocaine	8	88.9	5	16.7	16.25	1	*< 0.001**
Heroine	1	11.1	1	3.3	0.86	1	0.354
Amphetamines	7	77.8	7	23.3	8.92	1	*0.003**
Benzodiazepines	3	33.3	0	0.0	10.83	1	*< 0.001**
Others	1	11.1	1	3.3	1.02	1	0.313

ADHD attention-deficit/hyperactivity disorder, *OCD* obsessive compulsive disorder, *SUD* substance use disorder, *PTSD* posttraumatic stress disorder, *SC* synthetic cannabinoid, *NC* natural cannabis, χ² Pearson's chi-squared test, *df* degrees of freedom, *p* p value

†Multiple categories can apply

*Italic, significant comparison (0.05 level)

and this difference was also significant. Moreover, SC users were significantly more often smokers and reported significantly more frequently lifetime history of amphetamine, benzodiazepine, and cocaine use compared with NC users without SC consumption.

Correlation Analysis

SC Use

A significant correlation was found for SC consumption and smoking ($r(58) = .367$, $p = .004$) as well as experience with specific drugs, including cannabis ($r(58) = .308$, $p = .017$), cocaine ($r(58) = .651$, $p < .001$), amphetamine ($r(58) = .512$, $p = .000$), and benzodiazepines ($r(58) = .546$, $n = 60$, $p < .001$).

NC-Only Use Without SC

NC-only use showed significant correlations with smoking ($r(49) = .422$, $p = .002$).

Logistic Regression Analysis

Logistic regression analysis of the association between SC use and various sample characteristics yielded a model in which SUD and male were predictive for SC consumption in the analyzed sample (see Table 4).

Logistic regression analysis of the association between NC-only use and various sample characteristics yielded a model in which male sex and age were positive predictors for NC lifetime consumption, whereas ADHD medication was found as a negative predictor for NC consumption in the investigated ADHD sample (see Table 5 for further detail).

ADHD Symptom Severity

The study sample mean ADHD-SR score was $M = 28.33$ ($SD = 10.40$), and the mean WURS-k score was $M = 35.33$ ($SD = 14.23$).

In the SC-group, the mean ADHD-SR score was $M = 35.89$ ($SD = 11.32$, range 18–49) and the mean WURS-k scores was $M = 53.89$ ($SD = 14.42$, range 32–75). Patients in the NC-only group reached an average ADHD-SR score of $M = 27.43$ ($SD = 9.32$, range 9–51) and a mean WURS-k score of $M = 32.06$ ($SD = 11.53$, range 13–51).

The Shapiro-Wilk test revealed that the results in the ADHD-SR ($W(60) = 0.97$, $p = .129$) and WURS-k ($W(60) = 0.96$, $p = .232$) questionnaires were normally distributed within the sample. ADHD patients, who reported SC consumption in lifetime history, reached significant higher results in both questionnaires (ADHD-SR $t(58) = -2.463$, $p = .017$; WURS-k $t(58) = -5.046$, $p = .000$) than ADHD patients without SC consumption (see Fig. 2). With regard to NC consumption, no significant difference was found in the ADHD-SR ($t(49) = -3.8$, $p = 0.71$) or WURS-k ($t(49) = -0.55$, $p = 0.59$) questionnaires between NC-only users and NC nonusers.

Discussion

Available studies on the prevalence of SC consumption among psychiatric populations remain limited. To our knowledge, this prospective clinical study is the first assessing the prevalence of SC use in a well-characterized ADHD population and the first comparing consumer profiles

Table 4 Logistic regression analysis of variables predicting lifetime SC use. Male sex and SUD were predictors of SC lifetime consumption in ADHD patients

		B	SE	Wald	df	Sig.	Exp (B)	95% CI for Exp (B)	
								Lower	Upper
Last model	Sex	1.888	1.299	2.114	1	0.146	6.608	0.518	84.264
	SUD	2.899	0.968	8.964	1	0.003	18.161	2.722	121.179
	Intercept	−5.819	2.577	5.099	1	0.024	0.003		

SC synthetic cannabinoids

Table 5 Logistic regression analysis of variables predicting lifetime NC use. Sex and age were positive predictors of NC lifetime consumption in ADHD patients. Current ADHD medication intake was a negative predictor of NC lifetime consumption

		B	SE	Wald	df	Sig.	Exp (B)	95% CI for Exp (B)	
								Lower	Upper
Last model	Sex	1.315	0.807	2.653	1	0.103	3.724	0.765	18.120
	Age	0.087	0.044	3.794	1	0.051	1.090	0.999	1.190
	ADHD medication	−2.945	0.848	12.056	1	0.001	0.053	0.010	0.277
	Intercept	−3.193	1.888	2.862	1	0.091	0.041		

ADHD attention-deficit/hyperactivity disorder

of SC versus NC users in ADHD patients. The findings of this study reveal a relevant rate of 15% lifetime SC consumption among patients with ADHD. A previously published study of Welter et al. (2017), which was conducted at the same university hospital as the present study, found a SC consumption rate among psychiatric patients without ADHD of 7.2%. In comparison to previous investigations (see Table 6), the SC consumption rate found in patients with ADHD needs to be considered as high. According to national and regionally representative surveys, a lifetime prevalence of SC use in the general population between 0.2 and 4% was found (Loeffler et al. 2016). For Germany, general population-based data revealed a 0.8%
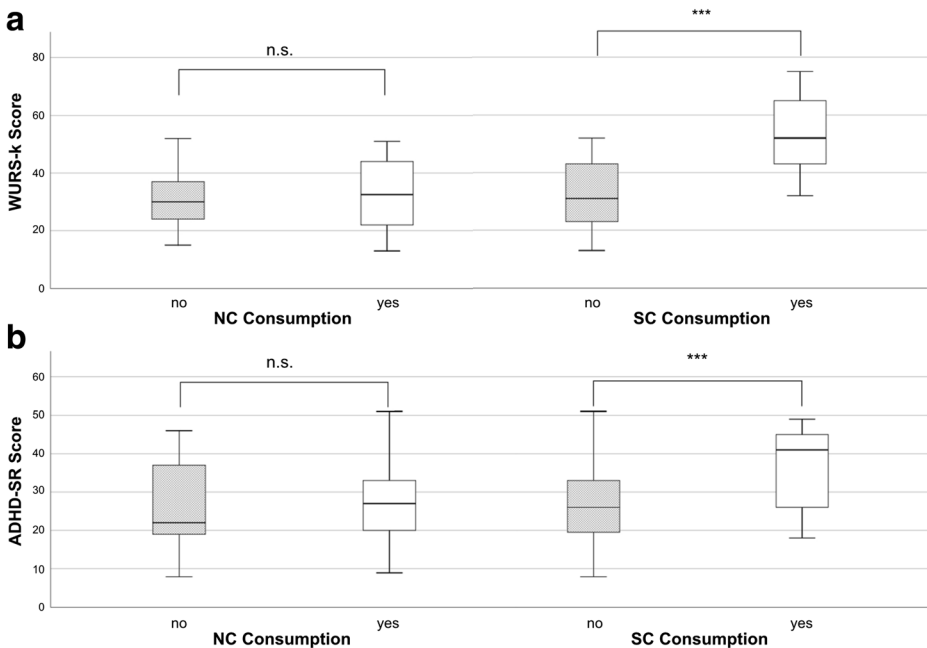
Fig. 2 Comparison of ADHD symptoms severity in the ADHD sample (*n* = 60): NC and SC users versus nonusers. Box-plot of the results in WURS-k and ADHD-SR questionnaires. Lower and upper box boundaries show 25th and 75th percentiles, respectively, line inside box depicts median, box contains the middle 50% of records, error lines displaying minimum and maximum values. NC, natural cannabis; SC, synthetic cannabinoids, WURS-K, Wender Utah Rating Scale (in German), ADHD-SR (German Version), ADHD Self-Rating Scale; n.s., not significant; ***$p < 0.001$

lifetime SC experience in adults in 2009 (Kraus et al. 2010). This prevalence increased up to a 2.6% lifetime NPS experience in 2018 (Seitz et al. 2019). Nevertheless, heterogeneous survey-based data complicates the comparability (European Monitoring Center for Drugs and Drug Addiction (2017). Therefore, the findings of this study need to be interpreted cautiously due to the overall small sample size and should be further evaluated in larger prospective studies.

Tobacco, alcohol, cocaine, and NC are known as the most frequently abused substances among ADHD patients (Biederman et al. 1995; Estevez et al. 2016). A recent study found ADHD and NC use to be partly determined by genetic factors, with a 70–80% estimated heritability of ADHD and 40–48% for NC initiation (Soler Artigas et al. 2019). Current data even suggests ADHD being causal related to lifetime NC use on a genetic basis (Soler Artigas et al. 2019). According to a large multisite study, 38% of adolescents with cannabis use disorder suffered from comorbid ADHD (Dennis et al. 2004). In the investigated ADHD sample of the

Table 6 Lifetime prevalence of SC consumption in the USA and European countries

Country	Year	Particular group	Age	Lifetime prevalence of SC consumption
USA	2012	Students	17–18	11.3%[1]
USA	2013	Students	17–18	7.9%[1]
USA	2014	Students	17–18	5.8%[1]
Spain	2010	Students	14–18	1.1%[1]
Spain	2012	Students	14–18	1.4%[1]
Spain	2013	General population	15–64	0.5%[1]
Spain	2014	Students	14–18	0.8%[1]
France	2014	General population	18–64	1.7%[1]
		Adults	18–34	4.0%[1]
		Adults	35–64	0.6%[1]
Sweden	2016	Students	9th grade	1.6%[1]
		Students	11th grade	3.2%[1]
Germany	2009	Students	15–18	7.0%[1]
	2010	Students	15–18	9.0%[1]
	2011	Students	15–18	7.0%[1]
	2012	Students	15–18	7.0%[1]
	2013	Students	15–18	5.0%[1]
	2014	Students	15- 18	6.0%[1]
	2015	Students	15- 18	6.0%[1]
Germany	2009	General population	18–64	0.8%[2]
		General population	18–24	2.5%[2]
Germany	2017	Psychotic patients	18–64	10.6%[3]
		Nonpsychotic psychiatric patients	18–64	4.5%[3]
UK	2010/2011	General population	16–64	0.2%[1]
	2011/2012	General population	16–64	0.1%[1]
UK	2012	Regular clubbers		5.0%[a]
UK	2016	Prisoners		33.0%[b]
UK	2015	Prisoners		10.0%[c]

USA United States of America, *UK* United Kingdom, *SC* synthetic cannabinoids

[1] European Monitoring Center for Drugs and Drug Addiction (2017)

[2] Kraus et al. (2010)

[3] Welter et al. (2017)

[a] Last year prevalence

[b] Last month prevalence

[c] Consumption in current prison

presented study, NC was the most frequently consumed illicit drug. In addition, every forth NC consumer reported SC experiences as well. The average age of first NC consumption was significantly lower compared with that of SC initiation, which confirms previous findings for NC (19.2 years of age) and NPS (22.4 years of age) initiation ages in survey-based data (Piontek et al. 2016). The results of this study revealed that all SC users of the analyzed population had been previous NC users. This is consistent with prior findings showing students with SC consumption being mostly experienced cannabis consumers (European Monitoring Center for Drugs and Drug Addiction 2017; Seitz et al. 2019). With regard to the consumer profiles, logistic regression revealed male sex as predictors for both SC and NC use. Among the SC users, the risk was 6.6-fold, in the NC users 3.7-fold higher in men than in women. This is consistent to the fact that SC and NC users are known to be mostly males (Kloos et al. 2009; Manseau et al. 2017). Furthermore, logistic regression found current ADHD medication intake as protective for NC, but not for SC lifetime consumption. In concordance, large longitudinal registry studies suggested medication for ADHD as protective against SUD (Chang et al. 2014; Lichtenstein et al. 2012). It needs to be discussed whether early diagnosis and treatment of NC consumption in ADHD patients might be able to prevent SC consumption in later life. This aspect merits further investigation in future studies.

ADHD is a known significant risk factor for substance abuse and the development of substance use disorder through the lifespan (Soler Artigas et al. 2019). Additionally, it is well known that comorbid SUD and ADHD patients often suffer from poly-substance use (Crunelle et al. 2018). In our sample, history of SC use in ADHD patients revealed a three times higher risk of suffering from SUD, than NC users with ADHD. Moreover, logistic regression showed SUD being predictive for SC consumption with an 18.2-fold higher risk for lifetime SC consumption, if ADHD patients having comorbid SUD. Our analysis reveal that patients, who already had lifetime experience with illicit drugs or suffering from SUD, are more likely to have contact with SC throughout their lifespan. This finding is consistent with previous studies showing an association of SC use with different, often several psychiatric comorbidities, and especially SUDs (Akram et al. 2019; Manseau et al. 2017). In further concordance, our results indicate that ADHD patients, who had lifetime experience with SC and NC, are significantly more likely suffering from more than one comorbid psychiatric disorders in comparison to NC-only users. This is particularly important since exposure to SC as well as NC during adolescence has been found to be associated with an increased risk of developing schizophrenia later in life (Cohen and Weinstein 2018). In spite of this, none of our participants showed symptoms of psychotic disorders.

SC and NC lifetime experiences correlated significantly with smoking in our sample. Tobacco use has already been found common among SC users (Gunderson et al. 2014). Furthermore, smoking is known to antecede the development of SUD in children and adolescents with ADHD (Kollins et al. 2005). It is discussed that nicotine exposure affects brain plasticity to an increased susceptibility of later SUD (Trauth et al. 2000). Data also suggest that one-half of ADHD adolescent smokers develop SUD in later life (Biederman et al. 2006). One reason may lay in the social factors like peer group pressure (Belendiuk et al. 2016), and higher availability to illicit substances through peer groups. In our study, nearly half of the SC consumers received SC through acquaintances as well.

In the SC, but not in the NC, group, patients scored significantly higher in both the WURS-k as well as in the ADHD-SR questionnaire. Our results suggest that severe childhood ADHD symptoms lead to SC consumption in adulthood. With regard to the childhood ADHD symptoms, previous studies found that adolescents with ADHD are at increased risk for SUD

with earlier onset (Zulauf et al. 2014). A meta-analytical review showed that childhood ADHD leads to a 1.5-fold higher likelihood of SUD compared with non-ADHD children (Charach et al. 2011). The risk for alcohol, NC, and nicotine dependence in adulthood is greater for those individuals with persisting ADHD (Breyer et al. 2014). Initiation of substance use in adolescents has been found to be likely better predicted by symptom severity (Ernst et al. 2006). Risk for smoking for example has already been described as having a linear relationship with ADHD symptoms, suggesting a dimensional rather than a categorical nature of SUD risk in adolescents with ADHD (Kollins et al. 2005; Wilens et al. 2008). The higher current ADHD symptoms in SC users may be contributed by the high rate of SUD in SC users compared with SC nonusers. Studies found that an active SUD can lead to an exacerbated ADHD symptomatology of 30%, so that in terms of diagnostic processes a period of abstinence or at least lower consumption is necessary (National Institute on Drug Abuse 2019; Wilens et al. 2011).

Finally, ADHD is significantly associated with a propensity to exhibit risky substance use patterns (Estevez et al. 2016). SC use with its unpredictable effects can be regarded as risky (Mills et al. 2015; Muller et al. 2016). Therefore, the high prevalence may also be contributed by the higher novelty-seeking (Donfrancesco et al. 2015) or rather risk-taking behavior of ADHD patients (Thapar and Cooper 2016). The most common cause for SC use is curiosity (Loeffler et al. 2016). Further generally known motives for first use of SC instead of NC include legality, availability, recreational effects, therapeutic effects, non-detection in standard drug screening assays, and reduction or cessation of cannabis use (Barratt et al. 2013). Our results could also hint at the self-medication hypothesis, which is regarded as one explanation for the high comorbidity of ADHD and SUDs (Khantzian 1997). According to the self-medication hypothesis, patients discover relief from or changes in symptoms through drugs and tent to self-administer these drugs (Khantzian 1997). Cannabis in particular is reported to provide relief for patients with the hyperactive/impulsive subtype of ADHD (Loflin et al. 2014). As SC are designed to imitate the effects of THC, unfortunately with unpredictable and more severe effects than NC (Kemp et al. 2016; Mills et al. 2015; Muller et al. 2016; Underwood 2015), ADHD patients who already have experience with relief from or changes in symptoms when taking cannabis, amphetamine, or cocaine may be seduced by SC as well. In terms of SC and their unpredictable toxicity and potentially poisonous side effects, this can be regarded as particularly dangerous (Kemp et al. 2016; Mills et al. 2015; Muller et al. 2016; Underwood 2015).

At present, a large range of SC with a high structural diversity and high variability of effects on the human body exists (Kemp et al. 2016; Miliano et al. 2016; Mills et al. 2015). As reported in our results section, we found a high variability in symptoms after SC consumption, especially gastrointestinal, neuropsychiatric, and cardiovascular symptoms, which were more frequently negative than positive. ADHD patients did not report specific side effects of SC use as similar symptoms have also been reported in previous studies on the side effects of SC (Mills et al. 2015; Muller et al. 2016). One of the five SC-consuming patients in our study reported having consumed SC along with other drugs and alcohol, which is one of the reasons SC use results in overdoses and mortality (Miliano et al. 2016). All of the SC consumers reported to have consumed the substances once or twice a month at maximum. None of the participants intended to consume SC again. Previous studies also showed that SC use tend to sustained quickly (Loeffler et al. 2016).

Unfortunately, questions regarding the consumption of SC are rarely routinely included in psychiatric interviews. Whether the SC use of ADHD patients is motivated by self-medication attempts, the higher novelty-seeking behavior (Donfrancesco et al. 2015), the risk-taking

behavior (Thapar and Cooper 2016), or by other sociodemographic or neurobiological reasons must be clarified in further studies.

Long-term effects of SC use are widely unknown, but regular SC consumption is supposed to lead to cognitive deficits (Kemp et al. 2016; Miliano et al. 2016). Especially impairments on executive function have been found in SC users compared with both NC and non-NC users (Akram et al. 2019; Cohen et al. 2017), and ADHD patients are particularly known to suffer from deficits in executive functioning (Thapar and Cooper 2016). Therefore, this study underscores the need for further trials investigating SC consumption in a larger ADHD sample with special focus on long-term effects of SC use on ADHD symptomatology.

Conclusion

This study presented evidence of the elevated risks for SC use in ADHD patients. As comorbid ADHD and SUD have an impact on the severity of addiction, the therapeutic outcome and risk of further psychiatric disorders (van Emmerik-van Oortmerssen et al. 2013), a complete investigation and psychoeducation of legal and illicit substance use, including SC, is absolutely necessary in the treatment of ADHD patients (Dirks et al. 2017). Questions about SC consumption should be asked as part of routine daily medical practice in the context of ADHD. As we found NC consumption anteceding SC use in all cases, ADHD patients in particular should be informed that SC differ dramatically from THC and are definitely not useful for self-medication. Our results indicate that SC use should be subject to scrutiny by clinicians treating adult ADHD patients, especially in cases with concurrent SUD.

Limitation

As a clinical, survey-based, prospective study, a limitation of our sample is that it was not balanced by sex or by SC vs. non-SC users. Instead, the lifetime prevalence of SC use in the analyzed ADHD sample was compared with estimated prevalence rates of SC use of previously published studies. Due to the overall small sample size of SC and NC user samples of this prospective study, results should be taken with caution and should be confirmed in larger trials.

Compliance with Ethical Standards

Statement of Ethics   All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients for being included in the study.
The study received appropriate ethics committee approval from the Ethics Commission of the School of Medicine and Health Sciences of the Carl von Ossietzky University of Oldenburg (CvO).

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Affiliations

Alexandra P. Lam [1,2] · Sebastian Moeller [1] · Christine Speitling [2] · Martin C. Lam [2] · Alexandra Philipsen [1] · Helge H. O. Müller [1,2,3,4,5]

✉ Alexandra P. Lam
   alexandra.lam@ukbonn.de

[1] Department of Psychiatry and Psychotherapy, University of Bonn, Venusberg-Campus 1, D 53127 Bonn, Germany

[2] School of Medicine and Health Sciences, Medical Campus University of Oldenburg, Oldenburg, Germany

[3] Division of Medical Psychology, University of Bonn, Bonn, Germany

[4] Department of Psychiatry and Psychotherapy Germany, Gemeinschaftskrankenhaus Herdecke, Gerhard-Kienle-Weg 4, 58313 Herdecke, Germany

[5] Chair of Integrative Psychiatry and Psychotherapy, Witten/Herdecke University, Alfred-Herrhausen-Straße 50, 58448 Witten, Germany