What are the psychological effects of using synthetic cannabinoids? A systematic review

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Abstract

Background: Synthetic cannabinoids (SCs), are typically full agonists at the cannabinoid CB1 receptor, therefore considerably more potent than natural cannabis (NC) and may have correspondingly more serious psychological effects. Despite government sanctions against their production they continue to be available in ever-increasing varieties over the internet. Psychological consequences of SC use are relatively unknown. Aim: To synthesise the available research on the psychological consequences of SC use. Method: A literature search of three databases was conducted in February 2018, including the following keywords: Spice, synthetic cannabis, cognition, affect, behaviour, psychosis, depression and anxiety. Results: Seventeen papers involving a variety of participants were eligible for inclusion: one controlled administration study, seven cross-sectional studies, five internet surveys and four qualitative studies. The controlled administration study showed that, compared to placebo SCs acutely affected some aspects of cognitive functioning and subjective psychological ratings. Non-controlled, cross-sectional studies generally showed that SC users performed lower on cognitive tasks and showed elevated symptomatology (e.g. paranoia) compared to both NC and non-cannabis users. Methodological limitations were noted across different study designs. There is limited research on how doses, frequency, or type of SC influence outcomes. Conclusions: Acutely SC use can result in a range of psychological outcomes, and when non-intoxicated SC users appear to differ from NC and non-users on various affective and cognitive domains. As SC use is increasing in at-risk populations there is an urgent need for more and better research to inform users, professionals and policymakers.

Keywords: Synthetic cannabis, psychological, behavioural, affective, cognitive, depression, anxiety, systematic review

Introduction

Synthetic cannabinoids (SCs) were first developed in the 1960s as researchers explored potential medical uses of compounds that targeted cannabinoid (CB1) receptors (Sedefov et al., 2009) . Over the past ten years SCs have been used recreationally and 179 different SC compounds have now been notified to the European Monitoring Centre of Drugs and Drug Addiction (EMCDDA, 2018). Common street names for these drugs include 'spice' or 'K2'. Despite the overall prevalence of SC use being relatively low (Van Amsterdam et al., 2013), their use by more marginalised social groups, such as homeless and prison populations (EMCDDA, 2018) is a concern. For example, a UK survey of 8 prisons reported the prevalence of 'spice' use within the previous month had increased from 10% in 2015 to 33% in 2016, with 46% of those users using almost daily (EMCDDA, 2017).

Effects of synthetic cannabis use

Whereas (9-tetrahydrocannabinol (THC), the main psychoactive component of natural cannabis (NC)), is a partial agonist at the cannabinoid receptors CB1 and CB2, most SCs act as full agonists at CB1 and are therefore much more powerful (Auwärter et al., 2009; EMCDDA, 2011) with a 4-5 times higher affinity (ElSohly et al., 2014) and a 40-660 times higher potency than THC (Van Amsterdam et al., 2015). It has therefore been suggested that the adverse side effects induced by SCs may be much more severe and occur more frequently than those induced by NC (Albertson et al., 2016; D'Souza et al., 2016; Gray et al., 2016; Van Amsterdam et al., 2015). In the media and online, it has been reported anecdotally that users appear like 'zombies' who can be seen staggering around unresponsive to the environment following SC use (Cooke and Birchall, 2018). To date, clinical research into the effects of SCs remains in its infancy with the literature consisting mainly of uncontrolled studies for both ethical and practical reasons.

Adverse physical health effects have been identified following SC use, including tachycardia, myocardial infarction, acute kidney injury, seizures and gastrointestinal problems evidenced from a mixture of case-reports and retrospective case note reviews (see Karila et al., 2016, Tait et al., 2016 and Weinstein et al., 2017 for reviews). A small number of case series have been published on the effects of SC on driving, including poor coordination, sedating effects, confusion and impairment of motor skills (Musshoff et al., 2014; Yeakel and Logan, 2013). In addition to these risks, prolonged use of SCs has been associated with withdrawal symptoms including agitation, anxiety and mood swings (Nacca et al., 2013). Fatalities have also been documented, with Tait et al., (2016) identifying at least 26 individuals who died following SC use. Potential mechanisms have included cardiac dysrhythmias or seizures, liver and kidney failure as well as indirect causes such as hypothermia (people found unconscious outdoors in winter); and jumping from a building (Tait et al., 2016). The current review focuses primarily on mental health.

Alongside increases in recreational SC use, there has been a surge of case reports of individuals with no pre-existing mental health conditions experiencing acute psychotic reactions as well as anxiety, suicidality and other adverse psychological reactions to SC use (see Cohen and Weinstein, 2018, Papanti et al., 2013, Karila et al., 2016 and Tait et al., 2016 for reviews). In some cases, these have resolved quickly with minimal intervention, in others, there have been persistent difficulties (Müller et al., 2010, 2016; Van der Veer and Friday, 2011; Wilkinson et al., 2014). Attempts to conduct larger scale research investigating these effects have mainly come from retrospective reviews of data from toxicology reports or poison hotline databases (Doğan et al., 2016; Forrester, 2011; Hermanns-Clausen et al., 2013, 2017; Hoyte et al., 2012; Waugh et al., 2016). This research has evidenced a wide range of adverse psychological symptoms including agitation, hallucinations and confusion. For example, a review in 2013 reported that increasing numbers of cases of acute psychosis following SC use, dubbed ‘Spiceophrenia’, were occurring (Papanti et al., 2013).

There is also evidence of worsening of mental health difficulties in individuals with pre-existing conditions. This comes from a mixture of case-studies (Celofiga et al., 2014; Leibu et al., 2013 for example) and retrospective case note reviews from records in psychiatric inpatient settings (Bassir Nia et al., 2016; Manseau et al., 2017; Shalit et al., 2016 for example). These indicate acute psychiatric symptomatology, in some cases requiring intervention, ranging from sedation to ECT and hospitalisation. The severity of psychiatric symptoms has been observed to be greater than that from NC user (Bassir Nia et al., 2016; Pereira et al., 2016; Shalit et al., 2016).

Given the potential of SCs to impact on the mental health of users, we carried out a systematic review of the existing literature to address the question: What are the psychological effects of SC use?

Method

Search Strategy

A search strategy was used to identify the relevant studies from the following electronic databases:

- Medline (1961 – February 2018)
- Cumulative Index to Nursing and Allied Health (CINAHL) (1904 – February 2018)
- PsycInfo (1806 – February 2018)

The search terms consisted of two main concepts, synthetic cannabinoids and psychological outcomes. The following keywords related to synthetic cannabinoids were used in the searches:

Spice OR K2 OR synthetic cannabis OR synthetic marijuana OR legal marijuana OR JWH

The following keywords related to psychological outcomes were used:

Psychological OR Psychiatric OR Cognition OR Neurocognition OR Affect OR Mood OR Behaviour OR Mental health OR Psychosis OR Schizophrenia OR Paranoia OR Hallucination OR Anxiety OR Panic OR Depression.

The syntax was amended to include functions such as * to allow for variations of forms of words to be searched at once, depending on the electronic database requirements. For example, synthetic cannabi* to allow for cannabis and cannabinoid.

Inclusion and Exclusion Criteria

Studies assessing the impact of SCs on psychological outcomes across behavioural, affective and/or cognitive domains were included. Methodologically, controlled administration, cross-sectional, qualitative studies and surveys were included; case-reports or case series and studies solely analysing case notes or existing databases were excluded. Studies had to be published in English, in peer-reviewed journals before February 2018. There was no restriction on the setting (e.g. inpatient, forensic settings, high schools).

Study Selection and Data Extraction

<Insert Figure 1 about here>

Figure 1: PRISMA diagram showing the review process

Results from the literature searches were exported into Endnote, a reference management software. Duplicate records were removed and the titles and abstracts were then screened for eligibility based on the inclusion criteria. The full-text of the remaining articles were then reviewed by the researcher (HA) who determined whether each study met inclusion criteria. Full details of the review process are shown in the PRISMA flow diagram (Figure 1).

Quality Assessment

The Standard Quality Assessment Criteria, QualSysts (Kmet et al., 2004) was chosen to assess study quality as it can be applied across various study designs. The tool consists of 14 questions for quantitative studies and 10 for qualitative, and not all questions apply to all study designs. From the ratings given for each question, a summary percentage score can be produced which is then comparable across study designs. Two independent raters conducted the quality assessment. Where there were disagreements papers were discussed and ratings were jointly agreed. The quality assessment was not used to determine study eligibility in the review but is reported to inform the interpretation of findings.

Results

1661 records were identified from the database search. After duplicates were removed and titles screened, 233 abstracts and full-text articles were reviewed. Subsequently, 216 records were excluded due to not meeting the review inclusion criteria (Figure 1).

Study Description

Table 1 shows a summary of the studies' characteristics, including country, design, population, sample size and quality assessment rating.

Overall, 17 papers were included in the study: 1 experimental study, 7 cross-sectional studies, 5 online surveys and 4 qualitative studies. Eight studies utilised comparison groups or conditions in their design. All included studies were published between 2011 and 2018 reflecting the recency of the development and use of these drugs.

Table 1:

Descriptive information and quality assessment rating for all studies included in the review

Reference	Country	Population	Sample size, total n	Comparison group/condition	QualSysts rating (%)
Controlled Administration Studies					
Theunissen, et al. (2018)	The Netherlands	Healthy volunteers	6	Yes	89
Cross-sectional Studies					
Altintas, et al. (2016)	Turkey	Psychiatric inpatients	81	Yes	86
Blevins, et al. (2016)	USA	Adolescent cannabis users	252	Yes	75
Bonar, et al. (2014)	USA	Substance use treatment centre residents	396	Yes	75
Clayton, et al. (2017)	USA	High school students	13 624	Yes	96
Cohen, et al. (2017)	Hungary and Israel	Substance use treatment centre residents and psychiatric inpatients	122	Yes	86
Gunderson, et al. (2014)	USA	Adult cannabis users	42	No	57
Welter, et al. (2017)	Germany	Psychiatric inpatients	332	Yes	75
Internet Surveys					
Barratt, et al. (2013).	Australia	Users of SCs	316	No	71

Vandrey, et al. (2012).	Global	Users of SCs	168	No	61
Winstock, and Barratt (2013a)	Global	General population	14 966	No	57
Winstock, and Barratt (2013b)	Global	General population	15 200	Yes	76
Winstock, et al. (2015).	Global	General population	21 656	No	71
Qualitative Studies					
Every-Palmer (2011)	New Zealand	Forensic inpatients	15	No	25
Kassai, et al. (2017).	Hungary	Drug rehabilitation service users	6	No	75
Soussan, and Kjellgren (2014)	Sweden	Online drug forum users	254	No	75
Van Hout and Hearne (2017)	Republic of Ireland	Dependent SC users	6	No	60

Controlled Administration Studies

There has been one experimental study to date, where 6 healthy experienced cannabis users were each administered two doses of a SC compound (JWH-018 2 & 3mg) and placebo via inhalation in a within-subjects design (Theunissen, et al. 2018, see Table 2 for details). The authors spent several years to obtain ethical approval for this study given the practical hazards and ethical concerns of administering SCs to young, healthy participants. The study is clearly underpowered and therefore generalisations from these findings are limited (Theunissen et al., 2018).

The participants were given a series of questionnaires and cognitive tests and monitored for 12 hours following inhalation of the SC. Compared with placebo, JWH-018 significantly increased tracking errors when following a moving target on a screen, in both the Critical Tracking Task (CTT) and Divided Attention Task (DAT), indicating poorer motor performance. The SC also slowed stop-signal reaction times on the Stop Signal Task (SST), indicating impaired response inhibition. However, these significant differences were only found following a summation of the scores of the cognitive measures across all post-drug test times, although there was no clear justification of this, lowering the quality of the study. Executive function, spatial memory and information processing did not show any significant differences between the three conditions. Further, there were no clinically significant changes recorded from physical vital signs or ECG patterns across the three conditions.

Subjective ratings of feeling 'high' showed that participants felt more 'high' at one and two hours after administration of the low-dose SC compared to placebo, but this was not significant following the high dose. Subjective 'high' scores correlated positively with concentrations of JWH-018 in serum after both SC doses. The Visual Analogue Scale (VAS) also included a measure of 'highness' and this was significantly higher after the low dose compared to both the placebo and high dose. Similarly, the VAS composite of external perception, measuring the level of misperception of an external stimulus, was higher

for the low dose compared to the high. The Profile of Mood States (POMS) showed that participants reported greater fatigue at 5 and 12 hours after administration of the high dose compared to the placebo, alongside increased ratings of arousal at 12 hours following the low dose compared to both placebo and the high dose.

Notably, many of the significant differences were between the 2mg dose and placebo, with fewer significant differences between the placebo and the 3mg dose or between the 2mg and 3mg doses. This could imply an inverse dose relationship. Pharmacokinetics showed serum levels of the SC were unexpectedly very low, had no clear dose-concentration relationship and indeed, were lower after the 3mg than the 2mg dose. This may have reflected the ineffectiveness of the method by which the drug was ingested as the authors report JWH-018 residue in the pipes used for inhalation and post-hoc testing revealed that up to 70% of active drug was not inhaled. This as well as the low sample size is clearly a methodological limitation of this study.

Table 2:

Experimental study: demographic data and outcome measures

Reference	Sample size (n)	Age mean (SD)	Gender % male (n)	Substance and detection method	Cognitive test Information processing	Motor performance	Divided attention	Response inhibition	Executive function	Spatial memory	Subjective effect questionnaires Subjective high	Mood	Psychedelic effects	Dissociation
Theunissen, et al. (2018)	6	23.5 (3.57)	33.3 (2)	JWH-018, urine and blood tests	Digit symbol substitution	Critical tracking task	Divided attention task	Stop signal task	Tower of London	Spatial memory task	Subjective high rating on a visual analogue scale	Profile of mood states	Bowdle visual analogue scales	Clinician administered dissociative states scale

Cross-Sectional Studies

Seven cross-sectional studies were included in the review and are detailed in Table 3a.

Table 3a

Cross-sectional studies: Group definitions, demographic data and outcome measures employed

Reference	Groups (n)	Age mean (SD)	Gender % male (n)	Inclusion criteria	Psychological outcomes
Altintas, et al. (2016)	Psychosis following SC use (50)	25.9 (5.5)	100 (50)	Self-report SC use for at least 4 months, not acute intoxication, no previous psychiatric diagnosis.	Brief Psychiatric Rating Scale Positive and Negative Syndrome Scale Frontal Assessment Battery (including subscales of conceptualisation, mental flexibility, programming, sensitivity to interference, inhibitory control and environmental autonomy) Hamilton Rating Scale for Depression Hamilton Anxiety Rating Scale
	Schizophrenia (31)	42.9 (11.6)	100 (31)	No personal or family history of SU and a diagnosis of schizophrenia	
Blevins, et al. (2016)	Lifetime SC use (72)	15.70 (1.02)	72.2 (52)	Self-report SC use ever	Subjective effects (for those who had used SCs within the past 60 days, n=15)
	No lifetime SC use (180)	15.87 (0.94)	66.7 (120)	Self-report no SC use ever	

Bonar, et al. (2014)	Lifetime SC use (150)	30.0 (9.8)[a]***	62 (93)	Self-report SC use ever	Beck Depression Inventory Global Severity Index, Paranoid ideation and Psychoticism subscales from the Brief Symptom Inventory (BSI)
	No lifetime SC use (246)	37.7 (10.2)[a]***	70 (172)	Self-report no SC use ever	
Clayton, et al. (2017)	Lifetime SC use (1554)		57.8 (892)[b]*	Self-report SC use ever	Health risk behaviours including questions on mental health: Have you ever felt sad or hopeless; seriously considered attempting suicide; attempted suicide.
	Lifetime NC only (4585)		50.8 (2329)[b]*	Self-report NC use ever and no SC use	
	Non-use (9049)		50.0 (4525)[b]*	Self-report no NC or SC use ever	
Cohen, et al. (2017)	SC users (38)	26.57 (7.90)	76 (29)	Regular SC use on a monthly basis with minimal usage of at least 10 times in the last year.	Beck depression inventory Spielberger state-trait anxiety inventory Computerised tasks: N-back task (working memory, matching of symbols in a 1-back or 2-back condition).
	NC users (43)	26.98 (5.37)	53 (23)	NC use more than 10 times in the last year and no SC use in the last year.	

	Non-C users (41)	25.56 (3.03)	54 (22)	No NC or SC use in the last year.	The Stroop task (inhibition, naming of colours of words in matching and non-matching conditions). Buschke Selective Reminding task (free recall of 16 bi-syllabic words following a diversion task).
Gunderson, et al. (2014)	Regular NC users who use SC (21)			Regular NC users who have used SCs ever	Questions on subjective effects, withdrawal and adverse effects
Welter, et al. (2017)	SC users (21)	25.6 (6.8)	71.4 (15)	Self-reported SC use	Modified Positive and Negative Symptom Scale: 9 symptom measures (persecutions, delusions, disorganisation, hallucinations, grandiosity, motor retardation, blunted affect, poor rapport and emotional withdrawal) Psychiatric diagnoses.
	NC users (26)	31.8 (10.5)	61.5 (16)	Self-reported NC use	

=p<0.05 ; **p<0.01; ***p<0.001

[a] *Significant differences between the two groups found, test used not reported*

[b] *Significant differences between the three groups found with a* χ^2 test

As shown, studies varied in study populations, ranging from those with psychosis following SC use (Altinas et al., 2016) to adult (Cohen et al., 2017; Gunderson et al., 2014) and adolescent cannabis users who have ever used SCs (Blevins et al., 2016) to high school students who have used SCs and NCs (Clayton et al., 2017). In addition, all studies acknowledged an overlap between NC and SC use, with those having used SCs having typically also using NC.

From the studies by Bonar, Ashrafioun and Ilgen (2014) and Clayton et al., (2017) it appears that SC users are generally younger and more likely to be male than non-SC users. These two studies also reported on ethnicity and while one found that SC users were significantly more likely to be white (Bonar et al., 2014) the other found that they were less likely to be white (Clayton et al., 2017). However, this difference may be related to their different study populations: high school students (Clayton et al., 2017) compared to substance use disorder patients in treatment (Bonar et al., 2014).

Table 3b

Cross-sectional studies: psychological well-being and cognitive outcomes

Reference	Groups (n)	Overall psychological distress	Psychotic symptoms				Depression	Anxiety	Cognitive	
Altintas, et al. (2016)			*BPRS*[a] *Mean (SD)*	*PANSS*[b] *overall Mean (SD)*	*PANSS- Mean (SD)*	*PANSS+ Mean (SD)*	*HRSD*[c] *Mean (SD)*	*HARS*[d] *Mean (SD)*	*FAB*[e] *Mean (SD)*	
	SC induced psychosis (50)		37.6 (13.7)	98.6 (24.8)	18.0 (6.5)[n]**	28.3 (7.1)	14.5 (7.2)	17.8 (10.3)[o]**	10.7 (3.7)	
	Schizophrenia (31)		32.5 (9.1)	91.1 (16.5)	22.3 (6.0)	26.0 (5.4)	12.0 (7.5)	11.4 (9.4)	12.1 (4.3)	
Blevins, et al. (2016)			*Paranoia % (n)*		*Hallucinations % (n)*			*Nervous/Panicky % (n)*	*Thought differently % (n)*	*Less coordinated % (n)*
	SC use in the past 60 days (15)		67 (10)		40 (6)			53 (8)	67 (10)	67 (10)

Reference	Groups (n)	Overall psychological distress	Psychotic symptoms		Depression			Anxiety	Cognitive
Bonar, et al. (2014)		*GSI*[f]	*Paranoid ideation (BSI*[g]*)*	*Psychoticism (BSI)*	*BDI*[h]				
		Mean (SD)	*Mean (SD)*	*Mean (SD)*	*Mean (SD)*				
	Lifetime SC use (150)	1.26 (0.79)[p]***	1.43 (0.99)[p]***	1.29 (0.94)[p]***	24.9 (11.8)[p]***				
	No lifetime SC use (246)	0.94 (0.79)	0.99 (0.89)	0.97 (0.94)	20.0 (12.8)				
Clayton, et al. (2017)					*Sadness*	*Suicidal ideation*	*Suicide attempt*		
					%	*%*	*%*		
	Ever used SC (1554)				47.5[q]*	32.7[q]*	22.0[q]*		
	Ever used NC only (4585)				36.8	22.2	11.1		
	Non-users (9049)				23.5	13.3	5.4		

Reference	Groups (n)	Overall psychological distress	Psychotic symptoms	Depression	Anxiety	Cognitive			
Cohen, et al. (2017)				*BDI*[h]	*SSTAI*[i]	*n(1)-back*[j]	*n(2)-back*[k]	*Stroop*[l]	*BSR*[m]
				Mean (SD)	*Mean (SD)*	*Mean (SD)*	*Mean (SD)*	*Mean (SD)*	*Mean (SD)*
	SC users (38)			19.97 (10.95)[r.s***]	53.39 (11.04)[r.s***]	75.4 (24.34)[r.s*]	67.94 (21.37)[r.s*]	1078.52 (356.58)[r.s*]	7.00 (2.46)[r.s*]
	NC users (43)			5.76 (4.97)	39.24 (9.08)	97.25 (3.99)	91.54 (7.41)	869.62 (172.43)	10.43 (2.57)
	Non-C users (41)			5.80 (4.72)	39.13 (8.04)	97.39 (2.41)	90.56 (6.11)	870.53 (161.87)	11.05 (2.72)

Reference	Groups (n)	*Anxiety*	*Panic attack*	*Trouble thinking clearly*	*Fatigue*
Gunderson, et al. (2014)		*% (n)*	*% (n)*	*% (n)*	*% (n)*
	SC users (21)	14 (3)	10 (2)	38 (8)	5 (1)

Reference	Groups (n)	Overall psychological distress	Psychotic symptoms	Depression	Anxiety	Cognitive
Welter, et al. (2017)			*Diagnosis of a psychotic disorder* *%* *(n)*			
	SC users (21)		71.4 (15)			
	NC users (26)		61.5 (16)			

***=p<0.05 ; **p<0.01; ***p<0.001**

BPRS[a] = Brief Psychiatric Rating Scale
PANSS[b] = Positive and Negative Syndrome Scale
HRSD[c] = Hamilton Rating Scale for Depression
HARS[d] = Hamilton Anxiety Rating Scale
FAB[e] = Frontal Assessment Battery
GSI[f] = Global Severity Index
BSI[g] = Brief symptom inventory
BDI[h]= Beck Depression Inventory
SSTAI[i]= Spielberger state-trait anxiety inventory
n(1)-back[j] = n-back task, 1-back condition, % correct reported
n(2)-back[k] = n-back task, 2 back condition, % correct reported
Stroop[l] = The Stroop task, incongruent condition, reaction time (ms) reported
BSR[m]= Buschke Selective Reminding task, words recalled reported
[n] = Significant differences found between SC induced psychosis and Schizophrenia group, with a t-test
[o]= Significant differences found between SC induced psychosis and Schizophrenia group, with a Mann-Whitney U
[p]= Significant differences found between lifetime SC use and no lifetime SC use group, type of test not reported
[q] = Significant differences found between ever used SC and non-user group, with a linear contrast
[r]= Significant differences found between SC users and NC users, with an ANOVA
[s]= Significant differences found between SC users and non-C users, with an ANOVA

Psychosis and psychosis-related symptomatology: Table 3b summarises data on psychological outcomes across studies. Four studies assessed psychosis and psychosis-related symptomatology. Three involved psychiatric populations administered validated scales (Altinas et al., 2016; Bonar et al., 2014; Welter et al., 2017), with one of these also including a clinical diagnosis (Welter et al., 2017). The fourth study, asked SC users about a range of subjective effects following use, including psychosis-related experiences (Blevins et al., 2016). Participants then had to rate the frequency of with which specific effects were experienced.

Bonar et al., (2014) found that amongst individuals in residential substance use disorder (SUD) treatment, those with SC lifetime use had statistically significant higher scores than those with no history of SC use in psychological distress, paranoid ideation and psychoticism as measured by the Brief Symptom Inventory subscales. .

Welter et al., (2017) reported that 71.4% of their sample of inpatient psychiatric patients who used SCs were diagnosed with a psychotic disorder, compared to 61.5% of NC users. Further, positive symptoms including persecutions, delusions, disorganisation and hallucinations, as assessed via a modified version of the PANSS, were experienced by a higher proportion of SC users than NC users. Negative symptoms, including motor retardation, blunted affect and emotional withdrawal, were, in contrast, experienced by a higher proportion of NC users than SC users. Statistical analyses were not carried out on these data therefore it is unclear if these differences are significant. The authors also assessed severity of symptoms, and their findings suggested that amongst psychiatric patients SC users experience significantly less severe negative symptoms than NC users ($p=0.026$). There was no significant difference in the severity of positive symptoms between SC and NC users.

Altinas et al., (2016) used the full PANSS measure and similarly found that patients who developed psychosis following a history of SC use had significantly fewer negative symptoms compared to those with a diagnosis of schizophrenia but no history of SC use. A sub-group analysis was conducted looking at older

(>43 years) and younger (≤43 years) non-SC users separately. There was a significant difference in negative symptoms for both groups compared to SC users of all ages who developed psychosis, however these effects are in different directions. Those patients with no history of SC use over the age of 43 experience fewer negative symptoms than SC users and those under the age of 43 experiencing more. Similarly to Welter et al., (2017), levels of positive symptoms showed no significant group differences.

From the single-questions about specific subjective effects, Blevins et al., (2016) found that 67% of their sample had experienced paranoia and 40% hallucinations 'at least some of the time' following SC use.

Depression. was assessed in four studies. Three of these used various validated scales (Altinas, et al., 2016; Bonar et al., 2014; Cohen et al., 2017); the other used single questions (Clayton et al., 2017) about ever experiencing (yes/no) feeling sad, having suicidal thoughts or attempting suicide. From these questions, Clayton et al., (2017), found significantly higher reports of experiencing these symptoms only in those who had ever used SCs compared to those who had never used any type of cannabis. In addition, two studies found significantly higher scores on depression measures for SC users compared to non-SC users (Bonar et al., 2014) and non-cannabis users (Cohen et al., 2017). In contrast, Altinas et al., (2016) found no significant difference in depression scores between those who have developed psychosis with a history of SC use when compared to participants with a diagnosis of schizophrenia and no history of SC use.

Anxiety. Anxiety scales were administered in two studies (Altinas et al., 2016; Cohen et al, 2017). Altinas et al., (2016) found significantly higher scores in anxiety for participants with psychosis following SC use compared to patients with schizophrenia who had no illicit substance use history. These differences remained significant for patients over the age of 43, with anxiety being significantly higher in SC users. Conversely, compared to those under 43 years, anxiety appeared to be lower in SC users, however this was a non-significant difference. Cohen et al., (2017) found significantly higher anxiety scores for SC users compared to both NC users and non-cannabis user, however no comparison was made of age groups.

Cognitive tasks. Two studies administered cognitive tasks including tests of executive function, inhibition and long-term memory (Altinas et al., 2016; Cohen et al., 2017). Altinas et al., (2016) administered the Frontal Assessment Battery (FAB) to investigate differences in executive function with subscales of mental flexibility, programming, sensitivity to interference, inhibition control and environmental autonomy. They found no significant differences on any of the subscales between patients with psychosis following SC use and those with a diagnosis of schizophrenia. However, Cohen et al., (2017) found SC users to be significantly impaired in working memory, cognitive inhibition and long-term memory compared to NC users and non-users as measured by the n-back task (working memory), the Stroop task (response inhibition) and Buschke Selective Reminding task (BSRT; episodic memory) respectively, as defined in Table 3a. Specifically, the authors found significantly lower accuracy for SC users compared to NC users and non-cannabis users on the n-back and Stroop task; longer reaction times on the Stroop task (across matching and non-matching conditions); and significantly fewer words recalled on the BSRT task. The authors did note, however, that the SC user group had significantly fewer years of education compared to the NC users and non-cannabis users and this could have contributed to the group differences (Cohen et al., 2017).

Internet Surveys

Details of the 5 internet surveys, with information from a total of 3640 SC users, are given in Table 4. Both psychological and physical health symptoms have been reported as these are increasingly acknowledged to be inherently linked. These surveys do not employ validated measures but provide a useful overview of psychological effects and complications related to SCs through respondents indicating yes or no to different experiences. As seen in Table 4, the data suggests SC users responding to internet surveys tend to be predominantly male and in their mid-twenties.

A range of psychological and physical acute effects have been documented through these surveys. The most common of these, anxiety or panic were reported by 14% - 83% and breathlessness by 38% - 57% of participants. However, these ranges are so broad as to be relatively meaningless. Three surveys found the effects of SCs generally lasted for 1-2 hours (Barratt et al., 2013; Vandrey et al., 2012; Winstock and Barratt, 2013b). One survey compared effects between SC and NC users (Winstock and Barratt, 2013b). This showed significantly greater intensity of paranoia and significantly lower intensity of sedation, increased appetite and impaired memory reported after SC use compared to NC use.

Three of these studies utilise data from the Global Drug Survey which is run annually (Winstock and Barratt, 2013a, 2013b; Winstock et al., 2015). Both papers published in 2013 rely on data from the 2011 survey and therefore there is overlap in these findings. Although termed a 'global survey' the data generated tends to be from industrialised countries rather than low income countries.

Table 4

Internet surveys: sample size and population, demographics of the sample, psychological and physical symptoms reported

Reference	Sample size SC users	Inclusion criteria	Median Age (IQR)	Gender % male (n)	Psychological symptoms reported	Physical symptoms reported
Barratt, et al. (2013).	316	Australian residents, over 18, who reported SC use on one more prior occasions.	27 (23 - 34)	77 (243)	Dissociation (22%) Paranoia (18%) Panic (14%) Depression (4%) Psychosis (4%)	Decreased motor coordination (28%) Dizziness (20%) Headache (18%) Slurred speech (14%) Nausea and vomiting (9%)
Vandrey, et al. (2012).	168	Ever used SC		83 (139)	Hallucinations (28%) Nervous/anxious (54%) Paranoia (54%) Trouble remembering (64%)	Heavy/sluggish (63%) Vomited (10%)
Winstock, and Barratt (2013a)	23	SC users who sought Emergency Medical Treatment in the last 12 months			Panic and anxiety (82.6%) Paranoia (56.5%) Feeling scared (52.2.%) Seeing things (47.8%) Extreme agitation (34.8%) Hearing things (30.4%) Aggression (17.4%)	Breathing difficulties (56.5%) Very sweaty (52.2%) Chest pain (52.2%) Unable to talk (39.1%)

Winstock, and Barratt (2013b)	980	Use of SCs in last 12 months	23 (19 - 28)	79.6 (758)	Paranoia[a,***] Sedation[b,***] Increase in appetite[b,***] Impairment in memory[b,***]	
Winstock, et al. (2015).	2176	SC use in the last year	25 (20 - 34)	76.5 (1554)	n=21 (sought EMT) Panic and anxiety (81%) Paranoia (61%) Scared (61.9%) Agitation (47.6%) Auditory hallucinations (33.3%) Visual hallucinations (33.3%) Mood problems (28.6%) Aggression (9.5%)	n=21 Breathlessness (38.1%) Sweating (38.1%) Chest Pain (33.3%) Unable to talk (28.6%) Seizure /fits (19.0%) Bladder problems (9.5%)

*=p<0.05 ; **p<0.01; ***p<0.001

[a] = In comparison to NC users (n=975) significantly higher intensity

[b] = In comparison to NC users (n=975) significantly lower intensity

Qualitative Studies

Four qualitative studies were included in the review and these are summarised in Table 5. They focus on the experiences of using SCs (Kassai et al., 2017), developing SC dependence (Van-Hout and Hearne, 2017), adverse effects of SC use (Soussan and Kjellgren, 2014) and the interaction with psychosis (Every-Palmer, 2011).

A range of psychological effects were reported following consumption of SCs. Some quotes from the papers illustrating these effects are included below:

Anger: "Warm feelings, feel brilliant, but then when that feeling goes away, bad. Start feeling angry…." (Van-Hout and Hearne, 2017).

Paranoia: "I can't touch it, it makes me really paranoid… I felt that something bad was leaping out at me" – Male, occasional SC use (Every-Palmer, 2011).

Anxiety: "It made me feel like my world was closing in. It made me feel anxious and worried and my heart was pounding." – Male, occasional SC use (Every-Palmer, 2011).

Memory difficulties: "I tried watching Family Guy during intoxication, but the whole time I forgot what the episode was about." (Soussan and Kjellgren 2014).

Emotionally numb: "the drug totally distorted my personality, it turned myself inside out… it made me blunt, and switched off my brain" - 23-year-old male. (Kassai et al., 2017).

Mood changes: "When I smoked I was wallowing in self-pity, I felt sorry for myself, I was alone, I didn't care about anybody else, I hated everyone" – 20-year-old male. (Kassai et al., 2017).

Two papers reported themes about the unpredictability of both the physical and psychological effects of SCs (Kassai et al., 2017; Soussan and Kjellgren, 2014). In addition, two papers assessed effects across

different time points of use: acute intoxication, hangover, dependence and withdrawal (Kassai et al., 2017; Van-Hout and Hearne, 2017). For acute intoxication, frequent symptoms reported were tachycardia and respiratory difficulties, nausea and dizziness, warm and happy feelings, agitation, restlessness and fear and paranoia (Kassai et al., 2014; Van Hout and Hearne 2017). The most common symptoms reported during the hangover period were sluggish and dull feelings, tiredness and dehydration (Kassai et al., 2014). Dependence and withdrawal were characterised by memory and concentration impairments, mood swings, disconnection, aches and pains, anxiety, agitation and paranoia (Kassai et al., 2017; Van-Hout and Hearne 2017). In addition, Van-Hout and Hearne (2017) elicited a theme on self-detoxification attempts where participants described suicidal ideation and physical symptoms such as diarrhoea, insomnia and sweating.

Table 5

Qualitative studies: sample size and population, the method of data collection and analysis, the type or brand of SC, psychological and other outcomes reported

Reference	Sample size SC users	Population	Method of data collection and analysis	Type or brand of SC	Psychological effects	Other effects
Every-Palmer (2011)	15 Male 100%	Forensic inpatients identified by staff as having relapsed in the context of SC use.	Semi-structured interviews Thematic analysis	Aroma, Kronic, Skunk, Dream, Spice	Pronounced anxiety Psychotic relapse Paranoia	Shaking Dizzy Heart pounding
Kassai, et al. (2017).	6 Male 100% 20-27	Drug rehabilitation Self-identified SC users with problematic use for at least 2-6 years, abstinent for the past 1 month.	Semi-structured interviews Interpretative phenomenological analysis		Paranoia Relaxation Difficulty socialising Increased egoism Self-neglect Switch off brain Inability to sleep Feeling under control	Sweating

Soussan, and Kjellgren (2014)	254	Online drug forum users from one online forum	Internet posts on an online forum Thematic analysis		Sluggish/dull Disconnected and emotionally numb Fear and paranoia Panic attacks Disorientation Derealisation Mood swings Memory impairment Concentration difficulties	Nausea and dizziness Tachycardia and breathing difficulties Dehydration Muscle pain and tension
Van Hout and Hearne (2017)	6 SC dependent users 50% male	Dependent SC users as measured by the Severity of Dependence scale (scores above 7).	Semi-structured interviews Empirical Phenomenological Psychological five-step method	5f-AKB48 5F-PB-22	Agitation and restlessness Fear Paranoia Aggression Severe dissociation	Chest pain Aches and pains Palpitations Nausea Sweating Vomiting

Discussion

Overview

In this review we aimed to summarise the current evidence about the psychological effects of SC use. Previous reviews of the literature have focused on papers with small samples such as case-reports or case-series and research using information from poison hotline databases and toxicology reports (e.g. Brewer and Collins, 2014; Papanti et al., 2013). The current review aimed to outline the existing literature outside of these formats and this highlighted four main types of research methodology: controlled administration, cross-sectional, internet surveys and qualitative studies.

Unsurprisingly, there was a dearth of rigorous, peer-reviewed experimental research with controlled administration of SCs, with only one pilot study currently published (Theunissen et al., 2018). This was the first controlled study whereby a SC was administered with the intention of monitoring the cognitive and subjective effects of the drugs. Previous attempts have relied on self-experimentation from authors (Auwarter et al., 2009) or administration for developing technology to detect SCs in urine (Teske et al., 2010).

Acute SC intoxication can potentially result in impaired motor functioning, attention and response inhibition, but not have an effect on other executive functions, spatial memory and information processing (Theunissen et al., 2018). Interpretation of this study is hampered, however, given that serum levels of the drug were low and not dose-related, and the study lacked statistical power. The internet surveys provide a wealth of retrospective self-report data of the acute effects of SC use, with panic, anxiety, paranoia and breathlessness being reported most frequently (Barratt et al., 2013; Vandrey et al., 2012; Winstock and Barratt, 2013a; Winstock and Barratt, 2013b and Winstock et a., 2015). Similarly, the qualitative research provides a phenomenological account of the acute effects, with paranoia, fear and anxiety being mentioned in all of the studies (Every-Palmer, 2011; Kassai et al., 2017; Soussan and Kjellgren, 2014 and Van Hout

and Hearne, 2017). Given the diversity of methods used, and the limitations inherent in each of these, it is perhaps surprising that the acute effects reported are fairly consistent.

Individuals classified as SC users were found to have significant impairment in working memory, inhibition and long-term memory compared to NC and non-cannabis users (Cohen et al., 2017). SC users have been found to experience more anxiety, paranoia, psychoticism and depressive symptomatology compared to NC users and non-users (Bonar et al., 2014; Clayton et al., 2017; Cohen et al., 2017). In addition, SC users experiencing psychosis have been found to experience less severe negative symptoms and more anxiety than those with schizophrenia without co-morbid SC use (Altinas et al., 2016). Welter et al., (2017) found significantly greater positive symptoms and fewer negative symptoms in psychiatric patients using SC compared to those using NC only.

Methodological Limitations

This review highlights a range of methodological limitations with current published studies. The paucity of controlled human experimental research is notable. In the available uncontrolled research we cannot objectively know whether SC users are under the influence of any psychotropic drug. The controlled administration study is the only one where intoxication has been guaranteed (Theunissen et al., 2018). However, as they recruited a very small sample size due to ethical and practical limitations, this considerably limits the generalisability of the findings.

The cross-sectional research is variable in its quality, with a mean quality assessment rating of 78.5%. Studies ranged from using validated measures to less reliable, single-questions to evaluate psychological effects of SC use. In addition, the inclusion of participants always relied on retrospective self-report of SC use which introduces recall bias, whereby data may be unreliable. Furthermore, this method means these studies provide little information about the impact of specific compounds. No study blinded researchers to study group introducing further bias into the results and lowering the quality rating. Limited adjustments

for confounding factors were made across these studies, apart from an acknowledgement of age and education level in two studies (Altinas et al., 2016; Cohen et al., 2017 respectively). It is likely that there will be pre-existing differences between those who do and do not use SC that may contribute to mental health and cognitive differences, such as concomitant effects of other drug use, that are not accounted for by the current cross-sectional research.

The mean quality rating of the internet surveys was 67.2%. A methodological limitation across all included surveys, bringing down their ratings, was the reliance on uncontrolled and purposive sampling. The Global Drug Survey is widely advertised through magazines and newspapers internationally. This type of sampling creates a response bias, whereby those who take part are more likely to have a greater interest in or experience with drugs and may not be representative of the wider general population. Two surveys focus specifically on SC users and recruitment relied on advertisement in internet forums and on social media platforms where SCs are discussed, again inviting further bias (Barratt et al., 2013; Vandrey et al., 2012). The samples are likely to over-represent those who have an extensive drug use history and are more engaged with online discussion groups, therefore these findings may not be representative of the wider populations of SC users. All the surveys rely on retrospective self-reporting of symptoms during the acute phase of taking SCs which introduces recall bias into the results, making them less reliable. None of the included surveys attempt to capture specific compounds used therefore there is no way to attribute the effects reported to a specific form of SC.

The mean quality rating for the qualitative studies was 58.8%. Only two of the studies used verification procedures to establish the credibility of the analysis (Kassai et al., 2017; Soussan & Kjellgren, 2014) and none of the studies incorporated reflexivity bringing down the scores. In particular, one study undertaken in an inpatient setting relied on selection by staff and interviewing by a staff member, this may have had an influence on the participants' willingness to report the effects fully and honestly (Every-Palmer, 2011). In

addition, this study relied on interviews being recorded by hand and then made into longer notes once completed as participants declined audio recording. This will have introduced bias as what is recorded is shaped by what is remembered by the interviewer, which was not acknowledged in the paper.

Sampling is a key issue across the cross-sectional, survey and qualitative research. The most common approach is purposive sampling which introduces bias into the results, again reducing the generalisability of findings. There is clearly a difficulty in finding any individuals who only use SCs, as polydrug use is the norm and this potentially entails complex drug interactions. Where there are comparisons made with NC users, the frequent overlap between the use of the two drugs creates difficulty in associating effects with SC independently. In addition, research in specific vulnerable populations is limited, perhaps due to difficulties in sampling in these groups. We found only one study conducted in a forensic hospital setting (Every-Palmer, 2011) and no published research with homeless or prison populations where SC use is prevalent.

Another limitation of current research is the lack of biological confirmation of SC use from immunoassays of bodily fluids. The technology for this is not yet widely available and only one study discusses serum levels of SCs (Theunissen et al., 2018). Instead, studies are dependent on self-reporting of SC use and this reduces reliability as it introduces recall bias, especially important when the study retrospective memory of effects while the person is intoxicated with a memory impairing drug like SC and NC . In combination, the heterogeneity of the 179 SCs available, and the insufficient data on specific compounds or their doses in each study further limits the interpretation of findings. Only the controlled administration study (Theunissen et al., 2017) involved a specific SC compound. Van Hout and Hearne's (2017) study was the only other paper that specified certain compounds. However, the authors simply stated they recruited participants who said they use 5f-AKB48 and 5F-PB-22. However, no biological or other evidence of their use of these

specific drugs was gathered. Therefore, from only one study are we able to reliably draw conclusions about a specific compound, JWH-018 (Theunissen et al., 2018).

Review Limitations

The research reviewed is varied both in the research questions posed and the study population examined. A breadth of research questions have been collated, integrating findings of acute effects, from controlled administration and self-report data, with longer-term effects from psychological measures and cognitive tasks taken from those self-identified as SC users. Different studies also involved markedly different populations, from cannabis users in the general population (Blevins et al., 2016; Cohen et al., 2017; Gunderson et al., 2014) to those with diagnoses of serious mental illness (Altinas et al., 2016; Every-Palmer 2011) to dependent users and those engaged with drug treatment (Kassai et al., 2017; Van Hout and Hearne 2017) to high school students (Clayton et al., 2017). This clearly limits the integration of the findings across studies.

The majority of the reviewed studies do not differentiate between the psychological effects of SCs according to different usage patterns, which again limits the conclusions we can draw. Only two of the included studies specifically look at problematic (Kassai et al., 2017) and dependent (Van Hout and Hearne, 2017) users giving more useful information about this sub-group of the SC user population. In addition, two cross-sectional studies specify a certain level of use to be categorised as an SC user (Altinas et al., 2016; Cohen et al., 2017). Other than this, the research does not distinguish between those who have tried SCs once and those who use with differing degrees of regularity. In these cases, it is difficult to determine what psychological effects are related to the chronic, prolonged use of SCs.

In addition, is important to note that these studies come from a time period when SCs have undergone several changes to their legal status and classification internationally. Governments across the globe have attempted to stem distribution of SCs through increased legislation such as the Novel Psychoactive

Substances Act 2016 in the UK. This now makes it an offence to produce, supply or possess with intent to supply, any substance intended for human consumption that is capable of producing a psychoactive effect. This will have impacted on their production and availability of different compounds and the market continues to evolve today. Therefore, the review may not accurately represent the profile of psychological effects of SCs that are predominantly in circulation at the moment.

Clinical and Research Recommendations

Given the diversity of available SC compounds, the constantly changing composition even within brands, difficulties with detection and the limited available evidence highlighted from this review, making specific clinical recommendations is currently problematic. It is evident that SC use is becoming increasingly popular in some populations and actions taken by governments to reduce their availability appear ineffective. It is therefore imperative for clinicians working with at-risk populations - including homeless and prison populations - to be aware of SC use and its potential consequences in order to provide support and advice to users around the impact and risks it use can have.

Given that SC use is a relatively recent phenomenon it is apparent that it is an under-researched area. However, the continual growth of this market suggests that SCs will continue to be widely available via the internet, and therefore pose an ongoing risk. More rigorous evidence on the effects of SC use is needed to inform clinical decisions and policy making. It is key for clinicians to be involved in the research process going forward, to provide information and access to SC users to improve the existing evidence base.

Research methods need to be improved with the inclusion of biological confirmation of use, through testing samples, and an attempt to identify the specific compound used in order to inform the conclusions drawn. There is a need for more controlled lab studies looking at the acute effects of SC use. However as Theunissen et al., (2018) found, ethical approval for research with a large sample size is currently difficult to achieve due to the risks involved with administering SCs to participants. More naturalistic studies

prospectively monitoring the acute effects for users in their own homes may be possible as has been done in those using different natural cannabis varieties (for review see Curran et al, 2016).,

Cross-sectional research could be improved with larger samples and therefore higher powered studies to assess differences in psychological outcomes between groups of users and non-users. This research should attempt to adjust for the many potential confounding factors that may account for some of the group differences observed. Clearer categorisation in research of regular users compared to one-off users would also prove useful in mapping the prolonged psychological effects of SC use. There have been no longitudinal studies, following up large cohorts to map the effects of SC use prospectively over time, to date. Studies of this kind will prove useful in the future.

Conclusions

SC use is a growing concern and there is an urgent need to bring together current knowledge to inform users, healthcare professionals and policymakers. This review integrates findings from a range of sources to evidence what we understand about the impact of SCs at the moment. It is evident that SC use can result in a range of psychological outcomes as well as SC users being more impaired in behavioural, affective and cognitive domains, compared to NC and non-users. It also highlights the difficulties of capturing the effects of these compounds due to their ever-increasing variety and potential dangerousness. The latter has limited the possibility of large-scale controlled experimental research. Going forward, novel research methods with larger samples are needed if we are to better understand the psychological consequences of synthetic cannabinoids

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