Research report on

Adverse Mental Health Effects of a New Psychotropic Substance (Synthetic Cathinones): a Literature Review

Submitted to

Beat Drug Fund Association

Submitted by

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Abbreviations

3-MMC = 3-Methylmethcathinone

α-PVP = α-Pyrrolidinovalerophenone

APOC2: Apolipoprotein C-II

APOH: Apolipoprotein H

CBT: Cognitive behavioural therapy

CM: Contingency management

CRF: Corticotropin-releasing factor

DA: Dopamine

DAT: Selectively inhibits dopamine

DSM IV: Diagnostic and Statistical Manual of Mental Disorders, 4th edition

DSM V: Diagnostic and Statistical Manual of Mental Disorders, 5th edition

EEM: Exploratory eye movements.

GABA: Gamma aminobutyric acid

ICD-10: The International Statistical Classification of Diseases and Related Health Problems 10th Revision

MA: Methamphetamine

MDPHP = 3',4'-methylenedioxy-α-pyrrolidinohexanophenone

MDPV: 3,4-Methylenedioxypyrovalerone

MIP: Methamphetamine induced psychotic disorder

n: Number of participants

NMDA: N-Methyl-D-aspartic acid

NR: Not Report

PPS: Persistent psychotic symptoms

SC: Synthetic cathinones

SCUD: Synthetic cathinones use disorder

TPS: Transient psychotic symptoms

UK: United Kindom

US: United Sataes

VMAT2: Vesicular monoamine transporter

Origin and nature

Synthetic cathinones (SCs) are a large heterogeneous group of chemical analogues of the naturally occurring compound cathinone, which is the main psychoactive ingredient in the khat plant *Catha edulis*. The stimulant effects of khat have been known for centuries, and the practice of chewing khat leaves remains popular in many countries in East Africa and the Arabian Peninsula (Baumann et al., 2018). The subjective effects of khat leaf chewing include reduced fatigue and elated mood. The first export of khat to the United States, the United Kingdom, and elsewhere occurred in the mid-twentieth century (Oliver et al., 2018). In the 1970s, cathinone was isolated from khat leaves and identified as the primary psychoactive compound in this plant (Baumann et al., 2018). Cathinone was initially synthesised by medicinal chemists and investigated for its therapeutic potential. Some SCs have been approved for the treatment of anorexia, fatigue, and depression (Baumann et al., 2018). However, many other SCs are misused as drugs of abuse. From a structural chemical perspective, cathinone is the β-keto analogue of amphetamine, and therefore, synthetic cathinones are often referred to as bk-amphetamines. Hence, it is not surprising that SCs induce powerful psychomotor stimulant effects and are known to cause dependency (Baumann et al., 2018).

SCs constitute the second largest group of new psychoactive substances worldwide, including in Northeast Asia and China. The number of scheduled SCs has increased dramatically in the past few years (Lee et al., 2017). New SCs are continuously developed to circumvent legislative control, and by 2017, more than 100 SCs had been identified worldwide (Baumann et al., 2018). It has been estimated that nearly 250 new analogues are produced each year (Weinstein et al., 2017). SCs are most commonly prepared in the forms of powders or crystals, or less commonly, as tablets. Their packaging is intentionally labelled to resemble commercially available bath products, hence the use of the name ‘bath salts’ (Baumann et al., 2018). SCs have also been labelled as ‘plant food’, ‘plant feeders’, ‘research chemicals’, and ‘not for human use’, with product names including ‘blue silk’, ‘vanilla sky’, ‘white lightning’ (Oliver et al., 2018), ‘meow meow’, ‘bliss’, ‘energy-1’, ‘hurricane Charlie’,

'white rush', 'bloom', 'blue magic', 'cloud 10', 'mind candy', 'rocket fuel', 'sextasy', and 'torpedo' (Karila et al., 2015).

Pattern of recreational use

Most SCs are manufactured by Asian chemical companies and sold over the Internet (Baumann et al., 2018). SCs were probably used as recreational drugs for the first time in 2010 (Baumann et al., 2018). The typical SC users are young adults who are either employed or in school and have a history of stimulant and polydrug use (German et al., 2014). SCs are abused for social and economic reasons, in addition to their stimulant and hallucinogenic properties, often serving as replacements for ecstasy, cocaine, and amphetamines (German et al., 2014). In a survey of schools and universities in Scotland, 20.3% of respondents reported that they had previously used SCs, while 4.4% reported daily use (Weinstein et al., 2017). A survey of high school students in the US found that 1.3% of students reported SC use during the previous year (Oliver et al., 2018). In a survey of electronic dance music party attendees, 7.7% reported that they had used SCs (Oliver et al., 2018). A 2011 survey of attendees of gay-friendly nightclubs in London revealed a lifetime SC use rate of 63.8% (Karila et al., 2015).

SCs are consumed via oral ingestion, inhalation, or snorting (Weinstein et al., 2017). They are commonly used in a binge manner in social settings (e.g., friends' homes, house parties, or night clubs) (German et al., 2014), and are often consumed concomitantly via several routes of administration during a single session (Thornton & Baum 2014). SCs are frequently combined with other substances, such as alcohol, cocaine, ecstasy, cannabis, or ketamine. The primary effects sought by users include increased alertness, empathy, euphoria, openness in communication, talkativeness, intensification of sensory experiences, music sensitivity, reduced appetite, increased sexual performance, and increases in sociability and work capacity (Karila et al., 2015). Low doses of SCs produce typical stimulant effects, such as increased energy and alertness, increased sexual desire and risk-taking sexual behaviour, elevated mood, and euphoria. However, high doses or repeated use can induce serious symptoms, including hallucinations, psychosis, excited delirium accompanied by aggressive or violent behaviours, tachycardia, hypertension, hyperthermia, seizure, and death (Weinstein et al., 2017; Baumann et al., 2018). In a UK-based online survey, the majority of

respondents who had previously used cocaine reported that SCs provided a longer-lasting and better 'high' than cocaine, and the effects of SCs were considered comparable to those of ecstasy (Bretteville-Jensen et al., 2013). The perception that SCs are safer, more consistent, and more cost-effective than ecstasy or cocaine appears to drive preferences for SCs over other stimulants (German et al., 2014).

Pharmacology

SCs have been designed to mimic the effects of more traditional psychostimulants, such as cocaine, methamphetamine, or ecstasy (Leyrer-Jackson et al., 2018). In animal models, acute SC administration produces rapid increases in locomotor activity and stereotypy (German et al., 2014). Generally, SCs either block presynaptic monoamine (e.g., dopamine, norepinephrine, and serotonin) reuptake transporters or act as substrates for these transporters. The latter mechanism of action results in a substantial efflux of monoamines from presynaptic terminals (Leyrer-Jackson et al., 2018). Frequently, the transporter affinities of various SCs are expressed in terms of the dopamine/serotonin ratio, with higher values indicating a preferential affinity for dopamine and a higher potential to induce compulsive and abuse-like intake patterns. In contrast, lower dopamine/serotonin ratios indicate a preferential affinity for serotonin and generally entactogenic and episodic intake patterns similar to those observed with ecstasy (Leyrer-Jackson et al., 2018). Depending on the route of Belhadj-Tahar administration, the time to onset of the effects of SCs varies from less than 1 minute (smoking, vaporising, snorting) to 25 minutes (swallowing), and the durations of these effects range from 1 to 10 hours (Ashrafioun et al., 2016). SCs are not detected by routine urine toxicology screens (Baumann et al., 2013b).

Adverse reactions, intoxications, and deaths

SC use is associated with a high risk of severe adverse effects, including agitated delirium, psychosis, seizure, multiple organ failure, and death (Leyrer-Jackson et al., 2018). Cardiac, psychiatric, and neurological signs and symptoms are the most common adverse effects reported in synthetic cathinone users who require medical care. Agitation is the single most common psychiatric symptom of SC toxicity, and its presentations range from mild agitation to severe psychosis requiring chemical restraint (Prosser & Nelson 2012). The most common physical symptoms of SC toxicity include hyperthermia, hypertension, tachycardia, hyponatremia, nausea, vomiting, and chest pain. However, more serious symptoms of SC

toxicity, including liver failure, kidney failure, rhabdomyolysis, and the development of compartment syndrome, require substantial and prolonged medical treatment and may be fatal. Previous reports of fatal intoxications of SCs have been ascribed to direct (e.g., acute drug toxicity) and indirect (e.g., self-harm and bizarre/risky behaviour) causes (German et al., 2014).

Psychiatric disorders

In a previous study, 62% of patients seeking medical care after SC use reported adverse psychiatric effects (Prosser & Nelson, 2012). Chronic SC use can induce acute psychosis, hypomania, paranoid ideation, and delusions (Weinstein et al., 2017). Other common psychiatric effects include dependence, depression, anxiety, and cognitive impairment.

1. *Withdrawal/dependence*

In a web-based survey of 104 recreational users of SCs, 57% reported tolerance and 36% reported a sense of dependence on SCs (Ashrafioun et al., 2016). In a questionnaire survey of 205 students in the UK who had previously used SCs, 17.6% reported addiction or dependence (Dargan et al., 2010). A survey of 1,500 users of mephedrone, an SC, found that more than 50% considered the drug to be addictive (Prosser & Nelson 2012). In a telephone survey of 100 mephedrone users, more than 30% reported that they met more than three of the Diagnostic and Statistical Manual IV criteria for dependence, including increased tolerance, continued use despite related problems, and impaired control of use (Prosser & Nelson 2012). A physical SC withdrawal syndrome has not been reported, although users have reported feelings of depression and anxiety at the end of use (Prosser & Nelson 2012). In Italy, a baby born to a woman who used SCs chronically exhibited symptoms of neonatal withdrawal syndrome (Weinstein et al., 2017).

2. *Psychosis*

The development of acute psychosis is among the most common clinical effects associated with SC use. In a review of 81 SC users admitted to a specialised clinical toxicology unit, 12% exhibited prolonged psychosis (Romanek et al., 2017). In a review of 50 SC users in a forensic setting, 22% presented with psychotic symptoms (Diestelmann et al., 2018). In a

case series of 11 SC users admitted to a poisons unit, 36% exhibited delusion and/or paranoia (Roberts et al., 2017). In a case series of 236 patients exposed to SCs and admitted to two poisons centres, 40% experienced hallucinations, 36% exhibited paranoia, and 20% received antipsychotic medications (Spiller et al., 2011). In summary, 12%–40% of SC users who receive medical care exhibit psychosis and/or psychotic symptoms.

In many cases involving the side effects of SCs, patients suffer from extreme paranoia and visual and auditory hallucinations and may be self-injurious or homicidal (Banks et al., 2014). In a review of 42 individual case reports of SC-induced psychosis, 30 described bizarre behaviour, auditory and visual hallucinations, extreme paranoia, agitation, and aggression so severe that police officers were called to the scene (Stiles et al., 2015). In addition, patients have been known to experience severe delusions that last for 24–96 hours while under the influence of bath salts (Stiles et al., 2015). Many of these patients have also reported amnesia regarding their psychotic episodes (Banks et al., 2014). However, even first-time users of SCs can experience psychosis, and this side effect does not seem to correlate with the dose or route of ingestion. Certain drug-taking behaviours may contribute to the occurrence of SC-induced psychosis. These include (a) the use of bath salts containing multiple SCs; (b) mixing SCs with other street drugs or alcohol; or (c) mixing SCs with prescription drugs, including benzodiazepines, to increase the high (Stiles et al., 2015). Healthcare providers worldwide have reported difficulties in the diagnosis and treatment of bath salt-induced psychosis (Stiles et al., 2015). However, antipsychotics have been successfully utilised in the management of SC-induced psychosis (Banks et al., 2014).

3. Depression and suicide

Depression may occur as a direct effect of long-term SC use (Schifano et al. 2011). Symptoms of depression and anhedonia may result from the putative depletion of both serotonin and dopamine, consequent to SC use (Valente et al., 2014). Depression is also a symptom of SC withdrawal. In a laboratory study of regular SC users, the consumption of SCs for 3 days induced a persistent negative mood for several days after use (Homman et al., 2018). Lev-Ran (2012) described a young man with SC dependence and depression who required antidepressant therapy. In an online survey of 294 new psychotropic substance users, of whom at least 68% reported the frequent use of various SCs, 55% of the subjects reported that depression was the most frequently experienced problem (Sande., 2016). In an

online survey of 81 SC users, 87% reported that they felt depressed while recovering from SC use, with symptoms such as a decreased appetite (88%), lack of motivation (92%), and hopelessness (76%) (Jones et al., 2016). Finally, in a large online survey of UK clubgoers, 41% reported depression as an adverse effect of SC use (Capriola 2013).

Self-harm related to SC use has been ascribed to impulsivity, paranoia, and violent behaviour in response to vivid hallucinations or delusional thought patterns (Oliver et al., 2018). Hanging is the most common form of fatal self-harm associated with SC use, although gunshots, self-stabbings, repeated self-lacerations (including slitting one's own throat), and jumping from bridges have all been reported (German et al., 2014). Belhadj-Tahar and Sadeg (2005) reported a young woman who slipped into a coma following an SC overdose. Rojek et al. (2012) reported a 21-year-old man who was admitted to the hospital following the ingestion of 10 SC tablets to commit suicide. Finally, Klavž et al. (2016) reported a 38-year-old man, with a history of depression and SC dependency, who ingested SCs with suicidal intention. In a previous review, 6 of the 15 SC-related deaths were attributed to suicide (deRoux & Dunn 2017). In another review, 4 of the 43 SC-related deaths involved suicide (Weinstein et al., 2017).

SC use may also promote self-harm and suicide as a consequence of withdrawal-associated affective distress. The excitotoxicity induced by SCs may require days to normalise, during which depression and suicidal thoughts may emerge. Indeed, the term 'suicide Tuesday' emerged to describe the state of depressive withdrawal experienced days after the initial use of a drug (Oliver et al., 2018). In a case of fatal self-harm associated with SC use, a 21-year-old with no history of depression committed suicide 5 days after ingesting a powdered SC (Oliver et al., 2018).

4. *Anxiety*

Chronic SC use can lead to anxiety (Valente et al., 2014). SC users have reported a sense of anxiety at the end of use (Prosser & Nelson 2012). In a review of the medical records of 43 patients with SC intoxication, 59% exhibited agitation or anxiety upon admission (Franzén et al., 2018). In a case series of 89 patients who presented at an emergency department in Aberdeen, 40% reported anxiety or agitation (Regan et al., 2011).

The Swedish Poisons Centre received 150 calls concerning SC intoxication in 2008/2009, and clinicians reported anxiety as a clinical feature in 14% of these calls (Hägerkvist et al., 2010). Moreover, clinicians reported anxiety as a clinical feature in 15% of the 131 telephone calls made to the UK National Poisons Information Service regarding SC use (James et al., 2011).

In a web-based survey, 20% of 1,506 SC users reported negative effects, of which anxiety, panic, and palpitations were most common (Carhart-Harris et al., 2011). In an online survey of 294 new psychotropic substance users, at least 68% reported the frequent use of various SCs and 39% reported that a sense of fear and anxiety was the most frequent problem experienced (Sande 2016). Finally, another online survey of 81 SC users found that 79% reported 'anxiety' during SC use and 74% reported 'feeling anxious' while recovering from SC use (Jones et al., 2016).

5. Cognitive impairment

Habitual users of SCs have been reported to exhibit cognitive dysfunction (Leyrer-Jackson et al., 2018), including short-term memory impairment (Valente et al., 2014). In animal studies, repeated exposure to high doses of SCs led to impaired cognitive function in the domains of spatial working and recognition memory (Leyrer-Jackson et al., 2018). Acute administration of SCs to human polydrug users (including prior SC users) impaired short-term spatial memory while sparing divided attention and improving psychomotor reaction times (de Sousa Fernandes Perna et al., 2016). In a study of 20 SC users and normal controls, SC was found to impair prose recall. The acute effects of SC consumption include impaired working memory, but enhanced psychomotor speed and verbal and category fluency (Freeman et al., 2012). In another laboratory study of regular SC users, SC consumption for 3 days led to impaired cognition for at least 2 days after use (Homman et al., 2018). In a naturalistic study of 10 SC users and 16 non-users, the former exhibited relatively worse performance during verbal memory and verbal fluency tasks. Moreover, the users' performances deteriorated further at 48 hours after the last use of SCs (Herzig et al., 2013).

6. Treatment

The treatment of SC intoxication primarily involves supportive and symptom control measures. Although most patients are unable to name the specific abused drug, no drug-

specific antidote exists even if the users are capable of providing such a history (Thornton & Baum 2014). Therefore, treatment should focus on reducing agitation and psychosis (Banks et al., 2014). Although many affected patients will present with excited delirium, the clinician must strive to achieve chemical rather than physical restraint, as the latter has been associated with sudden death in individuals with stimulant-induced psychosis (Banks et al., 2014). Emergency departments most commonly use intravenous fluids, benzodiazepines, oxygen, and sedatives to treat SC intoxication (Thornton & Baum 2014). Benzodiazepines have been used, in addition to haloperidol and droperidol (Glennon et al., 2014), to sedate patients exhibiting agitation and seizure . In the majority of successfully treated cases of SC intoxication, benzodiazepines and antipsychotics have been administered together with general supportive care (Banks et al., 2014). SC abuse and addiction are multidimensional conditions that disrupt many aspects of an individual's life, and therefore, treatment is not simple. Typically, effective substance abuse treatments are comprehensive and incorporate different components that target particular aspects of the disorder.

Importance of the project

The use of SCs has spread in recent years and represents a new trend in substance use. The ever-changing nature of SCs has led to a situation wherein regulatory agencies are locked into a cat-and-mouse interplay with drug manufacturers and consumers. Most SC users are young men, and the strong risks of related abuse, addiction, and toxicity are matters of concern. Hence, SCs remain a topic of great interest for policy makers and practitioners in the field of drug addiction.

Objectives

The aim of this study was to identify the risk factors, frequency, symptoms, pathological mechanism, and treatment of SC-related psychiatric disorders (i.e., SCUD, psychosis, mood disorders, anxiety disorders, and cognitive impairment) via a comprehensive literature review.

Data sources

The principal investigator (WK Tang) conducted a Medline search in August 2020 using the keyword 'synthetic cathinones' to identify relevant articles (limits: English language, published between 1946 and 2020, human studies, abstracts available). In total, 1,192 articles were screened to exclude preclinical studies, review articles that had been superseded by more recent reviews, and other papers judged to be of lesser relevance to the study objectives. The reference lists of these articles were screened to identify further relevant articles. Finally, an additional search was conducted using individual SCs, such as mephedrone and MDPV, as keywords.

Data extraction

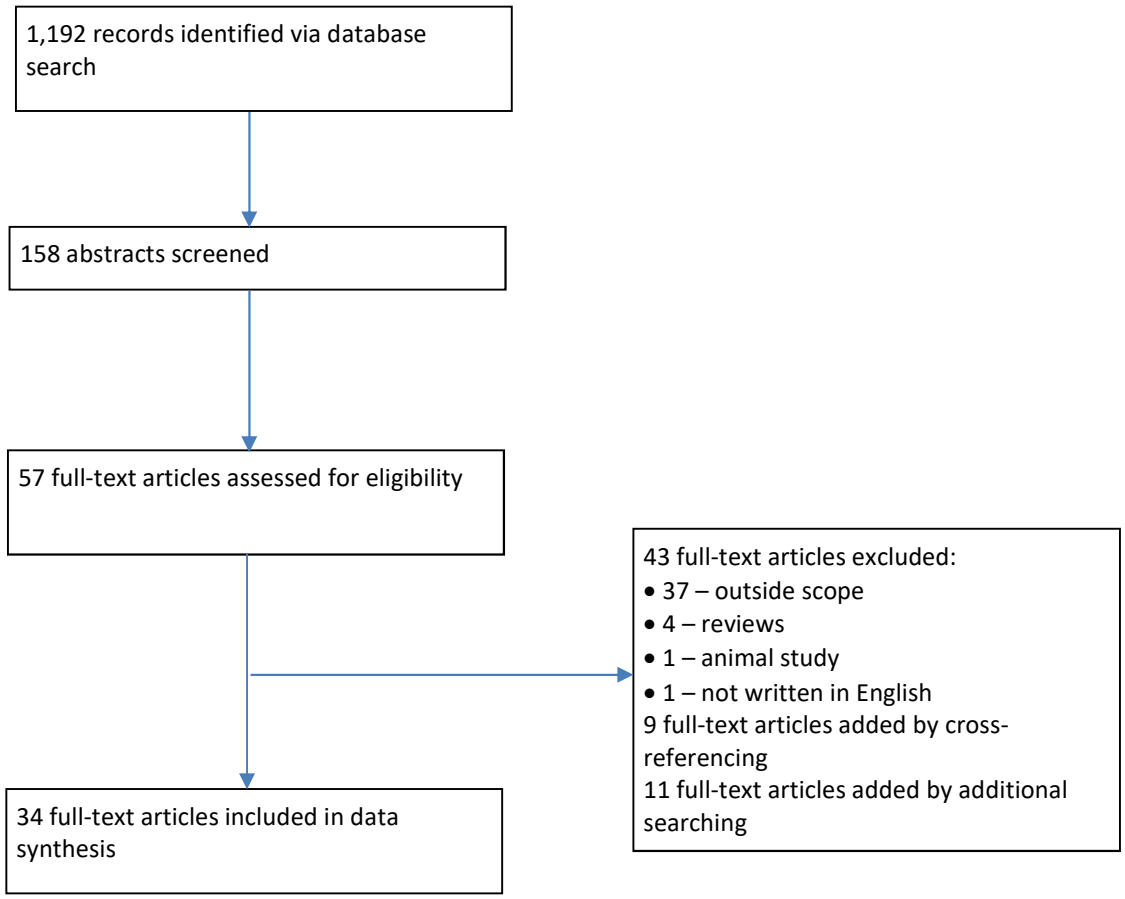
The principal investigator first screened the 1,192 titles and 158 abstracts. Of these, 1,135 articles failed to meet the eligibility criteria. Full-text versions of the remaining 57 articles were then screened by the principal investigator. This screening excluded a further 43 papers. Finally, to the remaining 14 articles, 20 articles were added by cross-referencing and additional searching (Figure 1).

Data synthesis

A standardised form was created to manage the data extracted from each eligible record. Information regarding the size, scope, sample, methods, and results of each study were entered by a research assistant and checked independently by the other investigators for accuracy and

completeness (Marshall & Werb, 2010).

Figure 1. Systematic search of English-language articles



Characteristics of use

Sources of SCs

In a study of 205 SC (mephedrone) users, the most common drug source was a dealer (49%) followed by the Internet (11%), a friend or family member (9%), free at a party (5%), and self-manufactured (1%). SCs were used in five different forms (tablet, capsule, powder, liquid, and crystal). Powders and capsules were the most commonly used forms of SC. In contrast, there was little reported use of liquid or crystalline forms (Dargan et al., 2010).

Patterns of use

In an online survey of 1,006 SC (mephedrone) users (80% male, mean age of 26 years), the modal number of lifetime uses was 11–50. The most common route of consumption was intranasal (57%), followed by oral (28%) and injection (7%) (Carhart-Harris et al., 2011). In an online survey of 113 SC (bath salts) users, 26% reported no use of bath salts in the past year. Of those who reported use in the past year (n = 84), 62%, 26%, and 12% of respondents reported using bath salts on 10 or fewer days (62%), 11–30 days (26%), or more than 30 days (12%). With regard to the number of times the drug was administered on a typical day of use, 22% reported use only once daily, 54% reported 2–5 administrations, 21% reported 6–20 administrations, and 4% reported more than 20 administrations (Johnson & Johnson 2014). In a survey of 947 ever users of SC (mephedrone), 15% reported consuming SC weekly or more often and 15.2% reported every 2 weeks, but the majority reported consuming SC monthly or less often (69.7%). Amongst those who reported SC use in the last month, the average

number of days of use was 4.3 days of the last 30 days, with 17% reporting use on 10 or more days, 3% reporting use on more than 20 days, and 0.4% reporting use on all 30 days (Winstock et al., 2011a). In a sub-sample of 100 users (average duration of SC use was 6 months), a typical session of use lasted for 10 hours (median), with an interval of 60 minutes (median) between doses. Eighty-two participants reported drinking alcohol, 36 used cannabis, 35 used ketamine, 26 used cocaine, and 23 used ecstasy. Forty-seven participants reported using mephedrone continuously for 48 hours or more, with a median of 3 days (Winstock et al., 2011b).

Motives for use

In a study of 100 SC users, the participants reported an average of 6 to 7 motives for SC use. The most common motives endorsed were related to recreational purposes, including to get high (58.5%), for experimentation or curiosity (46.8%), and because the user liked the feeling (42.6%). Other common motives included wanting to escape reality (42.2%) and simply because it was available (46.8%). Motives reflecting cognitive enhancement (14%), sexual enhancement (14%), and alleviation of physical symptoms (13%) were less commonly endorsed.

SC use disorder

Prevalence

The results of SCUD prevalence are shown in Tables 1 and 2. Nine cross-sectional studies (n = 4,318) examined the prevalence of SCUD, SC addiction, or SC dependence amongst SC users (Tables 1 and 2). Amongst the seven community-based cross-sectional studies, the prevalence of SCUD, dependence, or addiction ranged from 17.6% to 53%, with a weighted mean of 37% (Dargan et al., 2010; Carhart-Harris et al., 2011; Winstock et al., 2011b; Johnson & Johnson 2014; Uosukainen et al., 2015; Jones et al., 2016; Zimmerman et al., 2019). Amongst the two cross-sectional studies that involved selective samples, the prevalence of SCUD or dependence ranged from 33% in a case series of 21 SC abusers (Batisse et al., 2014) to 91% in a registry of 34 slammers (Schreck et al., 2020). SCUD symptoms were also examined in three studies involving community samples (Winstock et al., 2011b; Jones et al., 2016; Zimmerman et al., 2019).

Six cross-sectional studies (n = 3,126) examined the prevalence of individual SCUD or dependence symptoms, and all of these reported the frequencies of craving, tolerance, and withdrawal (Carhart-Harris et al., 2011; Winstock et al., 2011b; Uosukainen et al., 2015; Jones et al., 2016; Zimmerman et al., 2019; Schreck et al., 2020). The reported weighted means (ranges) of the frequencies of the observed symptoms are as follows: craving (four studies, n = 1,731, 40% [23%–69%]), tolerance (four studies, n = 1,649, 36% [23%–51%]), withdrawal (four studies, n = 1,549, 12% [10%–27%]), larger amount or longer duration of use (three studies, n = 1,539, 45% [44%–62%]), time spent (three studies, n = 1,539, 24% [20%–82%]), cut down (three studies, n = 1,539, 13% [12%–64%]), activities given up (three

studies, n = 1,539, 15% [7%-–52%]), social or interpersonal problems (two studies, n = 1,439, 14% [13%-55%]), hazardous use (one study, n = 34, 73%), physical or psychological problems (one study, n = 34, 70%), role failure (one study, n = 34, 58%), and continued use despite evidence of harm (one study, n = 34, 25%).

The limitations of the studies discussed above include the use of a cross-sectional design (Zimmerman et al., 2019); the use of selective samples, such as students (Dargan et al., 2010), individuals with known SC abuse (Batisse et al., 2014), or slammers (Schreck et al., 2020); a small sample size (Batisse et al., 2014); selection bias (Dargen et al., 2010); the lack of a control group (Carhart-Harris et al., 2011); no data on the typical SC dose (Johnson & Johnson 2014); the use of SCUD symptoms as an outcome (Schreck et al., 2020); self-reporting of symptoms and hence, uncertain accuracy of the responses (Carhart-Harris et al., 2011); recall bias (Uosukainen et al., 2015); and the use of Internet (Carhart-Harris et al., 2011) or telephone survey (Winstock et al., 2011b).

Risk factors

In an online survey of mephedrone users, younger (age < 25 years) users reported a higher prevalence of dependence, compared to older users, among both male (32.3% versus 16.7%) and female (35.5% versus 12.5%) users.

Neurobiology

There are no published data on the neurobiology of SCUD.

Clinical course

There are no published data on the clinical course of SCUD.

Treatment

It is problematic to draft a universally valid treatment/management plan for the medical, behavioural, and psychopathological disturbances related to the intake of almost several hundred different SCs identified here. Consumers of SCs may not be able to provide information about the substance(s) ingested, standard drug tests will show negative results, and sophisticated tests are not performed as part of typical clinical practice. Furthermore, neither gas chromatography–mass spectrometry nor gas chromatography–Fourier-transform infrared spectroscopy alone can successfully differentiate between all SCs (Shah et al., 2018).

Some SC users may simply need reassurance, support, and medical monitoring. The management of SC intoxication is typically directed at dealing with adverse effects as they arise. Due to the similarity of SCs with other stimulants, management strategies similar to those recommended for intoxication with those drugs may be effective. For example, if a diagnosis of SC-induced delirium is suspected, treatment efforts should focus on controlling agitation and then treating medical complications, such as metabolic acidosis (Schifano et al., 2012). Symptom-directed supportive care may also include the management of convulsions, hypertension or hypotension, and rhabdomyolysis. SC-associated serotonin syndrome, which is often associated with agitation, may be managed using both benzodiazepines and cyproheptadine (Shah et al., 2018).

The observation of asymptomatic patients should continue for several hours. When medication is needed, benzodiazepines may be the agents of choice. Agitated adults can be

sedated with an initial diazepam dose of 0.1–0.3 mg/kg body weight, by oral or intravenous administration. At times, larger doses or frequent re-dosing may be required to achieve an adequate sedative effect (Schifano et al., 2016). Further targeted treatment to control aggression and agitation may include intramuscular or intranasal midazolam, or intramuscular lorazepam. This approach may also be useful to stop seizures. If symptoms cannot be controlled with benzodiazepines alone, propofol and/or antipsychotics may be considered. In general, the use of atypical antipsychotics, including olanzapine, have shown good efficacy in containing episodes of aggression in different cohorts and at different phases of illness (Valeriani et al., 2015).

Finally, treatment for patients with chronic SC use should ideally include a drug management plan coupled with psychotherapy (De Sousa Fernandes Perna et al., 2016).

Table 1. Design of studies reporting SCUD symptoms

Study	Design	Participants	Follow-up	Outcome definition	Outcome diagnostic criteria/instrument	Outcome (%)	Definition of SC use	SC use (%)
Cross-sectional studies								
SCUD, abuse, or dependence in community samples								
Dargan et al., 2010	School, college, or university students	1,006 students	-	Addiction or dependence	Questionnaire	17.6% amongst mephedrone users	Ever used	20.3%
Carhart-Harris et al., 2011	Community sample	1,506 mephedrone users	-	Addiction	Web-based survey	52%	Ever used	100%
Winstock et al., 2011(b)	Community sample	100 mephedrone users	-	DSM-IV dependence symptoms	Telephone interview	-	Ever used	100%
Johnson & Johnson 2014	Community sample	110 SC users	-	SCUD	Online checklist	53%	Ever used	100%
Uosukainen et al., 2015	Community sample	1,405 mephedrone users	-	Dependence	Online survey, ≥ 3 DSM-IV dependence criteria	23.5%	Last year users	100%
Jones et al., 2016	Community sample	81 mephedrone users	-	SCUD symptoms	Online survey	Craving (69%)	Last year users	100%

Study	Design	Participants	Follow-up	Outcome definition	Outcome diagnostic criteria/instrument	Outcome (%)	Definition of SC use	SC use (%)
Zimmerman et al., 2019	Community sample	110 SC users	-	SCUD symptoms	Online questionnaire	-	Ever used	100%
SCUD, abuse, or dependence in selective samples								
Batisse et al., 2014	Case series of SC abuse	21 cases of SC abuse	-	SC dependence	DSM IV	33%	NR	100%
Schreck et al., 2020	A registry of slammers in France	34 slammers	-	SC dependence or SCUD	DSM IV or V	91%	NR	100%

DSM-IV = Diagnostic and Statistical Manual, 4th Edition
DSM-V = Diagnostic and Statistical Manual, 5th Edition
NR = Not reported
SC = Synthetic cathinone
SCUD = Synthetic cathinone use disorder
Slammers = men who have sex with men who intravenously inject drugs before or during planned sexual activity

Table 2. Findings of studies reporting SCUD symptoms

Study	Findings	Limitations
Cross-sectional studies		
SCUD, abuse, or dependence in community samples		
Dargan et al., 2010	Of the 205 users of mephedrone, 36 reported mephedrone addiction or dependence.	Selection bias, uncertain accuracy of responses, no formal assessment of SCUD
Carhart-Harris et al., 2011	Of the 1,506 users, 14% and 38% found mephedrone very and moderately addictive, respectively, and 39% reported craving.	Selection bias, uncertain accuracy of responses, lack of a control group, no formal assessment of SCUD
Winstock et al., 2011(b)	The frequencies of DSM-IV dependence symptoms were as follows: larger amount or longer duration (62.2%), tolerance (51.4%), continued use despite harm (24.5%), time spent (20.4%), cut down (14.3%), %), withdrawal (12.2%), and activities given up (7.1%).	Selection bias, polydrug use, self-reporting of symptoms, recall bias, no formal assessment of SCUD
Johnson & Johnson 2014	Of the 59 subjects with SCUD, 37%, 24%, and 39% met the criteria for mild, moderate, and severe SCUD, respectively. Eighty-one respondents endorsed the occurrence of at least one withdrawal symptom.	Small sample size, selection bias, uncertain accuracy of responses, no data on typical SC doses
Uosukainen et al., 2015	63.3% of subjects had at least one criterion of dependence. The frequencies of DSM-IV criteria were as follows: larger amount or longer duration (43.6%), tolerance (35.8%), time spent (22.8%), cut down (11.7%), activities given up (15.0%), social or interpersonal problems (12.7%), and withdrawal (10.3%).	Selection bias, polydrug use, amount of drug use not measured, self-reporting of symptoms, recall bias, no formal assessment of SCUD.
Jones et al., 2016	69% of subjects reported ‘craving for more’ as a recovery effect of mephedrone.	Selection bias, self-reporting of symptoms, recall bias, no formal assessment of SCUD

Study	Findings	Limitations
Zimmerman et al., 2019	The frequencies of tolerance, craving, and withdrawal symptoms were 23.4%, 23.4%, and 20.2%, respectively.	Selection bias, lack of a non-user control group, recall bias, no formal assessment of SCUD
SCUD, abuse, or dependence in selective samples		
Batisse et al., 2014	Seven patients presented with more than three substance dependence criteria.	Selective sample, small sample size, self-reporting of SC use
Schreck et al., 2020	The severity of SCUD was mild, moderate, and severe for 18%, 12%, and 58% of the patients, respectively. The median number of DSM diagnostic criteria met was 6 (0–11). The frequencies of DSM-V criteria were as follows: time spent (82%), hazardous use (73%), physical or psychological problems (70%), cut down or control (64%), role failure (58%), social or interpersonal problems (55%), activities given up (52%), larger amount or longer duration (52%), craving (45%), tolerance (42%), and withdrawal (27%).	Selective sample, severe cases of slammers were more likely to be reported, small sample size.

SCUD = Synthetic cathinone use disorder

Psychosis

Prevalence of psychosis and psychotic symptoms

The psychosis and psychotic symptom data are shown in Tables 3 and 4. Seven cross-sectional studies (n = 752) examined the prevalence of psychotic symptoms amongst SC users. Amongst the six community-based cross-sectional studies, the following psychotic symptoms were reported: paranoia (36%, 23%–65%, 706 [weighted mean, range, n]), hallucination (20%, 21%–22%, 424), visual hallucination (39%, 27%–66%, 285), auditory hallucination (30%, 22%–37%, 204), and odd beliefs (34%, 104) (Dargan et al., 2010; Winstock et al., 2011b; Johnson & Johnson 2014; Ashrafioun et al., 2016; Jones et al., 2016; Zimmerman et al., 2019).

Amongst five retrospective studies (n = 269), the prevalence of psychosis, drug-induced psychosis, prolonged psychosis, or confusion in SC users ranged from 9% to 43%, with a weighted mean of 14% (James et al., 2011; Froberg et al., 2015; Romanek et al., 2017; Grapp et al., 2020; Ling et al., 2020). Eighteen retrospective studies (n = 1,157) examined psychotic symptoms in SC users. The reported frequencies of psychotic symptoms ranged from 25% to 80%, with a weighted mean of 35% (n = 124) (Centers for Disease Control and Prevention 2011; Mackay et al., 2011; Regan et al., 2011; Spiller et al., 2011; Forrester et al., 2012; Forrester 2013; Batisse et al., 2014; Backberg et al., 2015; Beck et al., 2015; Beck et al., 2016; Fujita et al., 2016; Umebachi et al., 2016; Daveluy et al., 2017; Roberts et al., 2017; Beck et al., 2018; Diestelmann et al., 2018; Costa et al., 2019; Serre et al., 2019; Schreck et al., 2020). The following psychotic symptoms were reported: paranoia (27%, 6%–36%, 379 [weighted mean, range, n]) and hallucination (17%, 6%–40%, 751). In a study of 236 SC users, the frequency of catatonia was 1% (Spiller et al., 2011).

The limitations of the studies discussed above include the use of a cross-sectional (Zimmerman et al., 2019) and retrospective design (Serre et al., 2019); the use of selective subjects, such as arrestees (Diestelmann et al., 2018), individuals with known SC intoxications (Centers for Disease Control and Prevention 2011), or slammers (Schreck et al., 2020); a small sample size (Fujita et al., 2016); selection bias (Dargan et al., 2010); the lack of a control group (Johnson & Johnson 2014); no urine or blood analysis (Mackay et al., 2011); varied timing of clinical data acquisition and sample collection (Backberg et al., 2015); no data on the SC dose (Mackay et al., 2011); polydrug use (Winstock et al., 2011b); the use of psychotic symptoms as an outcome (Dargan et al., 2010); self-reporting of symptoms and hence, uncertain accuracy of the responses (Winstock et al., 2011b); and recall bias (Winstock et al., 2011b).

Risk factors

There are no published data on the risk factors associated with psychosis in SC users.

Neurobiology

There are no published data on the neurobiology of psychosis in SC users.

Clinical course and treatment

There is a lack of systematic investigations on the clinical course and treatment of SC-induced psychosis. However, some case reports have described the clinical course and treatment of SC-induced psychosis.

Thornton et al. (2012) reported a 23-year-old male with a prior psychiatric history who presented to the emergency department for bizarre behaviour, suicidality, and hallucinations after reportedly insufflating a bath salt. His psychosis and agitation resolved in a few hours after managing with lorazepam, droperidol, and observation in the emergency department (Thornton et al., 2012).

Bertol et al. (2014) reported a case of repeated 3,4-methylenedioxypyrovalerone (MDPV) consumption that resulted in severe psychosis and agitation. A 27-year-old man was found unresponsive in his apartment and was brought to the emergency department (ED) of a local hospital. When in the ED, he rapidly recovered and self-reported to have recently injected several doses of MDPV that he had purchased on the Internet. He left the hospital without medical care. Fifteen days later, he was again admitted to the same ED due to severe agitation, delirium, and hallucinations, and reported the use of MDPV and pharmaceutical drugs during the preceding week. He was sedated with diazepam and chlorpromazine. He was then admitted into a psychiatric ward, and aripiprazole was prescribed for regular use. After 10 days, the patient was discharged.

John et al. (2017) described a 40-year-old man with no past psychiatric history who presented with new-onset psychosis after ingesting bath salts. He purchased a gun and planned to shoot children in the neighbourhood who he believed were trespassers. He declined psychotropic management. His psychotic symptoms resolved after 12 days of inpatient treatment.

Bajaj et al. (2010) presented a case of psychosis in a patient using mephedrone for more than 1 year. The patient needed inpatient hospital care, was treated with the antipsychotic olanzapine, and recovered after 4 weeks of inpatient treatment.

Dolengevich-Segal et al. (2016) reported a 25-year-old man admitted into a psychiatric unit, presenting with psychotic symptoms after slamming mephedrone almost every weekend for the last 4 months. He presented with paranoid delusions, intense anxiety, and visual and kinaesthetic hallucinations. After 4 weeks of admission and antipsychotic treatment (paliperidone), the delusions completely disappeared.

Richman et al. (2018) described a 20-year-old male who developed drug-induced psychosis following the intake of an SC (α-pyrrolidinopentiophenone). He was hospitalised for 45 days and was treated with lorazepam and quetiapine. Upon discharge, he still had residual catatonic features (slowness) and mildly hyper-religious beliefs.

Penders et al. (2013) reported a case of persistent psychotic symptoms, despite discontinuation of use, including visual hallucinations, suspiciousness, and social withdrawal after several months of nasal insufflation of the SC MDPV. After failure to respond to treatment with several antipsychotic agents, the patient had a rapid and dramatic, although incomplete, response to electroconvulsive therapy. An 8-month follow-up report provided by the patient's outpatient psychiatrist indicated that she continued to have occasional hallucinations, but reported a diminished level of psychotic symptoms.

Barrio et al. (2016) reported a middle-aged man who reported 3 years of intravenous use of mephedrone. He used to binge for several days in a row. Psychotic symptoms, especially paranoid delusions, appeared after a few months. He was sent to aftercare in a therapeutic community, but his delusions kept reappearing after prolonged abstinence. A good response to risperidone was observed.

In summary, the duration of SC-induced psychosis varies between a few hours and several months. Some patients continue to have residual symptoms of psychosis, which can recur following further SC exposure. The psychosis is commonly treated with benzodiazepam (lorazepam or diazepam) and atypical antipsychotics (quetiapine, olanzapine, risperidone, paliperidone, or aripiprazole). In some patients, antipsychotic medication is not required, whereas in treatment-resistant cases, electroconvulsive therapy may be required to achieve symptom control.

Table 3. Design of studies reporting SC use and psychosis

Study	Design	Participants	Follow-up	Outcome definition	Outcome diagnostic criteria/instrument	Outcome (%)	Definition of SC use	SC use (%)
Cross-sectional studies								
Psychotic symptoms in community samples								
Dargan et al., 2010	School, college, or university students	1,006 students	-	Psychotic symptoms	Questionnaire	Paranoia (24.9%) and hallucinations (17.6%) amongst mephedrone users	Ever used	20.3%
Winstock et al., 2011(b)	Community sample	100 mephedrone users	-	Psychotic symptoms	Telephone interview	-	Ever used	100%
Johnson & Johnson 2014	Community sample	110 SC users	-	Psychotic symptoms	Online checklist	Paranoia (23%), hallucinations (21%)	Ever used	100%
Ashrafioun et al., 2016	Community sample	104 SC users	-	Psychotic symptoms	Online survey	Paranoia (42%), odd beliefs (34%), visual hallucinations (30%), auditory hallucinations (37%)	Ever used	100%

Study	Design	Participants	Follow-up	Outcome definition	Outcome diagnostic criteria/instrument	Outcome (%)	Definition of SC use	SC use (%)
Jones et al., 2016	Community sample	81 mephedrone users	-	Psychotic symptoms	Online survey	Seeing things (66%), paranoia (65%)	Last year use	100%
Zimmerman et al., 2019	Community sample	110 SC users	-	Psychotic symptoms	Online questionnaire	Paranoia (35.1%), hallucinations (22.3%)	Ever used	100%
Psychotic symptoms in selective samples								
Kapitany-Foveny et al., 2020	Clients attending an outpatient drug treatment centre	197 subjects	-	Psychotic symptoms	Brief Symptom Inventory	Paranoid ideation (5.6%), psychoticism (5.6%) **	Past year use	22%
Retrospective study								
Psychosis in selective samples								
James et al., 2011	Case series of SC toxicity	149 cases with mephedrone toxicity	-	Confusion or psychosis	Clinical history	13%	Report by health professionals	100%

Study	Design	Participants	Follow-up	Outcome definition	Outcome diagnostic criteria/instrument	Outcome (%)	Definition of SC use	SC use (%)
Froberg et al., 2015	Case series of SC intoxication	23 cases of MDPV intoxication	-	Psychosis	Clinical history	9%	Urine and blood analyses	100%
Romanek et al., 2017	Case series of SC toxicity	81 cases with SC toxicity	-	Psychosis lasting more than 24 hours	Clinical history	12%	Clinical history or laboratory confirmation	100%
Grapp et al., 2020	Case series of SC intoxication	Nine cases of MDPHP intoxication	-	Drug-induced psychosis	Clinical history	22%	Urine and blood analyses	100%
Ling et al., 2020	Case series of SC intoxication	Seven cases of N-ethylnorpentylone intoxication	-	Drug-induced psychosis	Clinical history	43%	Urine analysis	100%
Psychotic symptoms in selective samples								
Centers for Disease Control and Prevention 2011	Case series of SC intoxication	35 cases of 'bath salts' intoxication	-	Psychotic symptoms	Clinical history	Delusion or hallucinations (40%), paranoia (20%)	Clinical history	100%
Mackay et al., 2011	Case series of SC intoxication	20 cases with mephedrone toxicity	-	Psychotic symptoms	Clinical history	40%	Clinical history	100%

Study	Design	Participants	Follow-up	Outcome definition	Outcome diagnostic criteria/instrument	Outcome (%)	Definition of SC use	SC use (%)
Regan et al., 2011	Case series of SC toxicity	89 cases with mephedrone toxicity	-	Psychotic symptoms	Clinical history	Paranoia (6%), hallucinations (6%)	Clinical history	100%
Spiller et al., 2011	Case series of SC intoxication	236 cases of SC intoxication	-	Psychotic symptoms	Clinical history	Hallucinations (40%), paranoia (36%), catatonia (1%)	Clinical history	100%
Forrester et al., 2012; Forrester 2013	Case series of SC intoxication	362 cases of SC intoxication	-	Psychotic symptoms	Clinical history	Hallucinations (17.7%)	Clinical history	100%
Batisse et al., 2014	Case series of SC abuse	21 cases of SC abuse	-	Psychotic symptoms	Clinical history	46%	NR	100%
Backberg et al., 2015	Case series of SC intoxication	50 cases of 3-MMC intoxication	-	Psychotic symptoms	Clinical history	Hallucinations (20%)	Urine and/or blood analysis	100%
Beck et al., 2015	Case series of SC intoxication	193 cases of MDPV intoxication	-	Psychotic symptoms	Clinical history	Hallucinations (16%)	Urine and/or blood analysis	100%
Beck et al., 2016	Case series of SC intoxication	40 cases of α-PVP intoxication	-	Psychotic symptoms	Clinical history	Hallucinations (20%)	Urine and/or blood analysis	100%

Study	Design	Participants	Follow-up	Outcome definition	Outcome diagnostic criteria/instrument	Outcome (%)	Definition of SC use	SC use (%)
Fujita et al., 2016	Case series of SC intoxication	Three cases of SC intoxication	-	Psychotic symptoms	Clinical history	33%	Blood analysis	100%
Umebachi et al., 2016	Case series of SC intoxication	Eight cases of α-PVP intoxication	-	Psychotic symptoms	Clinical history	Hallucinations (25%), paranoia (25%).	Blood analysis	100%
Daveluy et al., 2017	Case series of SC intoxication	11 cases of SC intoxication	-	Psychotic symptoms	Clinical history	Hallucinations (36%), paranoia (18%)	+/− history urine and blood analyses	100%
Roberts et al., 2017	Case series of SC intoxication	11 cases of mexedrone intoxication	-	Psychotic symptoms	Clinical history	36%	Urine analysis	100%
Beck et al., 2018	Case series of SC intoxication	Eight cases of pyrovalerone derivative intoxication	-	Psychotic symptoms	Clinical history	25%	Urine and blood analysis	100%
Diestelmann et al., 2018	Case series of recent SC use in a forensic setting	50 cases of recent MDPV use	-	Psychotic symptoms	Clinical history	26%	Urine and blood analysis	100%
Costa et al., 2019	Case series of SC intoxication	Six cases of N-ethylnorpentylone intoxication	-	Psychotic symptoms	Clinical history	33%	Blood analysis	100%

Study	Design	Participants	Follow-up	Outcome definition	Outcome diagnostic criteria/instrument	Outcome (%)	Definition of SC use	SC use (%)
Serre et al., 2019	Case series of SC intoxication	Five cases of ephylone intoxication	-	Psychotic symptoms	Clinical history	80%	Analysis of drug	100%
Schreck et al., 2020	A registry of slammers in France	Nine slammers*	-	Psychotic symptoms	Clinical history	Hallucinations (11%)	NR	NR

3-MMC = 3-Methylmethcathinone
α-PVP = α-Pyrrolidinovalerophenone
MDPHP = 3′ ,4′-methylenedioxy-α-pyrrolidinohexanophenone
MDPV = 3,4-Methylenedioxypyrovalerone
NR = not reported
Slammers = men who have sex with men who intravenously inject drugs before or during planned sexual activity

*Only nine cases had psychotic symptoms recorded
**Percentage of subjects with prominent symptoms in individual dimensions

Table 4. Findings of studies reporting SC use and psychosis

Study	Findings	Limitations
Cross-sectional studies		
Psychotic symptoms in community samples		
Dargan et al., 2010	Of the 205 mephedrone users, 51 and 36 reported paranoia and hallucinations, respectively.	Selection bias, uncertain accuracy of responses, no formal assessment of psychosis
Winstock et al., 2011(b)	The frequencies of psychotic symptoms were as follows: paranoia (41%), visual hallucinations (27%), and auditory hallucinations (22%).	Selection bias, polydrug use, self-reporting of symptoms, recall bias, no formal assessment of psychotic disorders
Johnson & Johnson 2014	Some users reported paranoia (23%) and hallucinations (21%) 'every time' or 'most of the time' SCs were used.	Selection bias, self-reporting of SC use, lack of a non-user control group, no formal assessment of psychosis
Ashrafioun et al., 2016	Psychotic symptoms included paranoia, seeing things that are not there, hearing things that are not there, and unusual beliefs that others think are not true.	Selection bias, self-reporting of SC use, lack of a non-user control group, recall bias, no formal assessment of psychosis
Jones et al., 2016	66% of subjects reported seeing things and 65% reported paranoia.	Selection bias, self-reporting of symptoms, recall bias, no formal assessment of psychosis
Zimmerman et al., 2019	The prevalence of paranoia and hallucinations was 35.1% and 22.3%, respectively.	Selection bias, lack of a non-user control group, recall bias, no formal assessment of psychosis
Psychotic symptoms in selective samples		
Kapitany-Foveny et al., 2020	There were no significant differences in the proportion of subjects with paranoid ideation and psychoticism between SC users and non-SC users. SC users reported more	Retrospective self-reporting of SC use; no clinical diagnosis of psychosis

Study	Findings	Limitations
	paranoid ideation ($p < 0.01$) and higher psychoticism scores ($p < 0.001$), compared with non-SC users.	
Retrospective studies		
Psychosis in selective samples		
James et al., 2011	The prevalence of confusion or psychosis was 13% (21 out of 149).	Selective sample, prevalence of psychosis alone was not reported, indirect measurement, and possible under-reporting of psychosis
Mackay et al., 2011	Psychotic symptoms included auditory, visual, and tactile hallucinations; paranoid delusions; and thought block.	Selective sample, small sample size, chart review, polydrug use, no urine or blood analysis, amount of SC use unknown
Froberg et al., 2015	The prevalence of psychosis was 9% (2 out of 23).	Selective sample, referral bias, small sample size, chart review, polydrug use
Romanek et al., 2017	The prevalence of prolonged psychosis (>24 hours) was 12% (10 out of 81).	Selective sample, only 50% of cases had laboratory confirmation of SC use
Grapp et al., 2020	The prevalence of drug-induced psychosis was 22% (2 out of 9).	Selective sample, small sample size
Ling et al., 2020	The prevalence of drug-induced psychosis was 43% (3 out of 7).	Selective sample, small sample size, polydrug use
Psychotic symptoms in selective samples		

Study	Findings	Limitations
Centers for Disease Control and Prevention 2011	40% of cases had hallucinations or delusion and 20% had paranoia.	Small and selective sample, no formal diagnosis of psychosis
Mackay et al., 2011	Psychotic symptoms included auditory, visual, and tactile hallucinations; paranoid delusions; and thought block.	Selective sample, small sample size, chart review, polydrug use, no urine or blood analysis, amount of SC use unknown
Regan et al., 2011	6% of cases had hallucinations and paranoia.	Selective sample, no formal diagnosis of psychosis
Spiller et al., 2011	40%, 36%, and 1% of cases reported hallucinations, paranoia, and catatonia, respectively.	Selective sample, self- or informant-reporting of SC use, no formal diagnosis of psychosis
Forrester 2013	17.7% of cases reported hallucinations.	Selective sample, self- or informant-reporting of SC use, type of SC unknown, no formal diagnosis of psychosis
Batisse et al., 2014	Four patients reported terrifying hallucinations (auditory and visual).	Selective sample, small sample size, self-reporting of SC use
Backberg et al., 2015	The prevalence of hallucinations was 20% (10 out of 50).	Selective sample, limited clinical information, varied timing of clinical data acquisition and sample collection, polydrug use, no formal diagnosis of psychosis
Beck et al., 2015	The prevalence of hallucinations was 16% (31 out of 193).	Selective sample, limited clinical information, varied timing of clinical data acquisition and sample collection, polydrug use, no formal diagnosis of psychosis
Beck et al., 2016	The prevalence of hallucinations was 20% (8 out of 40).	Selective sample, limited clinical information, varied timing of clinical data acquisition and sample

Study	Findings	Limitations
		collection, polydrug use, no formal diagnosis of psychosis
Fujita et al., 2016	One case reported hallucinations and paranoia.	Selective sample, small sample size, no formal diagnosis of psychosis
Umebachi et al., 2016	The prevalence of hallucinations and paranoia was 25% for both symptoms.	Selective sample, small sample size, no formal diagnosis of psychosis, time between drug exposure and the hospital visit varied between subjects
Daveluy et al., 2017	The prevalence of hallucinations and paranoia was 36% and 18%, respectively.	Selective sample, small sample size, no formal diagnosis of psychosis
Roberts et al., 2017	The prevalence of psychotic symptoms was 36% (4 out of 11).	Selective sample, small sample size, polydrug use, limited clinical information, no formal diagnosis of psychosis
Beck et al., 2018	The prevalence of psychotic symptoms was 25% (2 out of 8).	Selective sample, small sample size, limited clinical information, varied timing of clinical data acquisition and sample collection, no formal diagnosis of psychosis
Diestelmann et al., 2018	Psychotic symptoms included somatic and visual hallucinations, and persecutory belief.	Selective sample, small sample size, no formal diagnosis of psychosis, concurrent use of other substances
Costa et al., 2019	One case reported disconnected speech and visual hallucinations, while the other one showed paranoia and symptoms of psychosis.	Selective sample, small sample size, no formal diagnosis of psychosis, concurrent use of other substances
Serre et al., 2019	Psychotic symptoms included paranoia, auditory hallucinations, and delusional states.	Selective sample, small sample size, no formal diagnosis of psychosis

Study	Findings	Limitations
Schreck et al., 2020	The prevalence of hallucinations was 11% (1 out of 9).	Selective sample, severe cases of slammers were more likely to be reported, small sample size

Bipolar disorders

The results of bipolar disorders are shown in Tables 5 and 6. Six cross-sectional studies (n = 1,452) examined the prevalence of manic symptoms amongst SC users. The following manic symptoms were reported: increased energy (97%, 94%–99%, 285 [weighted mean, range, n]), talkativeness (97%, 96%–98%, 181), hyperactivity (94%, 100), fast thoughts (91%, 104), euphoria (85%, 66%–98%, 395), excitement (60%, 33%–97%, 191), increased sexual drive (60%, 42%–79%, 1,261), inability to control laughter (10%, 110); anger or aggression (10%, 100) (Winstock et al., 2011a; Winstock et al., 2011b; Johnson & Johnson 2014; Ashrafioun et al., 2016; Jones et al., 2016; Zimmerman et al., 2019). One retrospective study reported a manic symptom frequency of 24% in SC users.

The limitations of the studies discussed above include the use of cross-sectional (Zimmerman et al., 2019) and retrospective designs (Diestelmann et al., 2018); the use of selective samples, such as arrestees (Diestelmann et al., 2018); a small sample size (Diestelmann et al., 2018); selection bias (Winstock et al., 2011b); the lack of a control group (Ashrafioun et al., 2016); no data on the SC dose (Johnson & Johnson 2014); polydrug use (Winstock et al., 2011a); the use of manic symptoms as an outcome (Johnson & Johnson 2014); self-reporting of symptoms and hence, uncertain accuracy of the responses (Winstock et al., 2011b); recall bias (Jones et al., 2016); and no formal diagnosis of bipolar disorder (Winstock et al., 2011a).

Risk factors

There are no published data on the risk factors for bipolar disorders in SC users.

Neurobiology

There are no published data on the neurobiology of bipolar disorders in SC users.

Clinical course and treatment

There are no published data on the clinical course and treatment of bipolar disorders in SC users.

Table 5. Design of studies reporting SC use and bipolar disorders

Study	Design	Participants	Follow-up	Outcome definition	Outcome diagnostic criteria/instrument	Outcome (%)	Definition of SC use	SC use (%)
Cross-sectional studies								
Winstock et al., 2011(a)	Community sample	947 mephedrone users	-	Manic symptoms	Online survey	Increased sexual drive (60%)	Ever used	100%
Winstock et al., 2011(b)	Community sample	100 mephedrone users	-	Manic symptoms	Telephone interview	-	Ever used	100%
Johnson & Johnson 2014	Community sample	110 SC users	-	Manic symptoms	Online checklist	-	Ever used	100%
Ashrafioun et al., 2016	Community sample	104 SC users	-	Manic symptoms	Online survey	-	Ever used	100%

Study	Design	Participants	Follow-up	Outcome definition	Outcome diagnostic criteria/instrument	Outcome (%)	Definition of SC use	SC use (%)
Jones et al., 2016	Community sample	81 mephedrone users	-	Manic symptoms	Online survey	Craving (69%)	Last year users	100%
Zimmerman et al., 2019	Community sample	110 SC users	-	Manic symptoms	Online questionnaire	Intensive excitement or happiness (33.0%)	Ever used	100%
Retrospective studies								
Diestelmann et al., 2018	Case series of recent SC use in a forensic setting	50 cases of recent MDPV use	-	Manic symptoms	Clinical history	24%	Urine and blood analyses	100%

Table 6. Findings of studies reporting SC use and bipolar disorders

Study	Findings	Limitations
Cross-sectional studies		
Winstock et al., 2011(a)	Some users reported an increase in sex drive (60%) after mephedrone use.	Selection bias, high rate of polydrug use, self-reporting of manic symptoms, no formal diagnosis of anxiety disorders
Winstock et al., 2011(b)	The frequencies of manic symptoms were as follows: increased energy (99%), euphoria (97%), talkativeness (96%), urge to move and do things (94%), increased sexual desire (66%), and anger or aggression (10%).	Selection bias, polydrug use, self-reporting of symptoms, recall bias, no formal assessment of bipolar disorder
Johnson & Johnson 2014	Some users reported feeling high (72%) or euphoric (66%), being more talkative (72%), an increased sex drive (42%), or being unable to control laughter (~10%) 'every time' or 'most of the time' SCs were used.	Small sample size, selection bias, uncertain accuracy of responses, no data on the typical SC doses, no formal diagnosis of bipolar disorder
Ashrafioun et al., 2016	Subjective acute effects of SCs included increased energy (94%), thoughts that are faster than normal (91%), happiness (85%), and increased sexual drive (79%).	Selection bias, self-reporting of SC use, lack of a non-user control group, recall bias, no formal assessment of bipolar disorder
Jones et al., 2016	Subjective acute effects of mephedrone included talkativeness (98%), excitement (97%), unusual amount of energy (97%), and euphoria (98%).	Selection bias, self-reporting of symptoms, recall bias, no formal assessment of mania
Zimmerman et al., 2019	33.3% of subjects reported intensive excitement or happiness after SC use.	Selection bias, lack of a non-user control group, recall bias, no formal assessment of bipolar disorder
Retrospective study		
Diestelmann et al., 2018	Manic symptoms included restless and irritable behaviour, hyperactivity, loquaciousness, mood swings, and euphoric behaviour.	Selective sample, small sample size, no formal diagnosis of bipolar disorder, concurrent use of other substances

Depression

The results for depression are shown in Tables 7 and 8. Five cross-sectional studies (n = 505) examined the prevalence of depressive symptoms amongst community-dwelling SC users. The following depressive symptoms were reported: lack of motivation (92%, n = 81), tiredness (90%, n = 100), reduced appetite (79%, 70%–88%, 291 [weighted mean, range, n]), irritability (77%, 64%–92%, 181), hopelessness (76%, n = 81); insomnia (71%, 45%–89%, 314), depressed mood (51%, 18%–87%, 285), reduced sex drive (24%, 17%–30%, 214), suicidal thoughts (12%, n = 110), decreased energy (7%, n = 104), and suicide attempt (3%, n = 110) (Winstock et al., 2011b; Johnson & Johnson 2014; Ashrafioun et al., 2016; Jones et al., 2016; Zimmerman et al., 2019). One cross-sectional study found that 36% of SC users (n = 43) attending an outpatient drug treatment centre had depressive symptoms (Kapitany-Foveny et al., 2020).

In a retrospective study (n = 20), the prevalence of depressive symptoms was 20% (Mackay et al 2011). The frequencies of individual depressive symptoms were as follows: low mood, 56% (n = 13); suicidal thoughts, 24% (11%–33%, n = 43); reduced appetite, 11% (n = 13); suicide attempt, 10% (n = 21); and weight loss, 8% (n = 13) (Batisse et al., 2014; Grapp et al., 2020; Schreck et al., 2020).

The limitations of the studies discussed above include the use of cross-sectional (Zimmerman et al., 2019) and retrospective designs (Mackay et al 2011); the use of selective samples, such as slammers (Schreck et al., 2020); a small sample size (Grapp et al., 2020); selection bias (Winstock et al., 2011b); the lack of a control group (Ashrafioun et al., 2016); no data on the SC dose (Johnson & Johnson 2014); the use depressive symptoms as an

outcome (Zimmerman et al., 2019); self-reporting of symptoms and hence, uncertain accuracy of the responses (Winstock et al., 2011b); recall bias (Winstock et al., 2011b); and no formal diagnosis of depression (Winstock et al., 2011b).

Risk factors

There are no published data on the risk factors for depression in SC users.

Neurobiology

There are no published data on the neurobiology of depression in SC users.

Clinical course and treatment

There are no published data on the clinical course and treatment of depression in SC users.

Table 7. Design of studies reporting SC use and depression

Study	Design	Participants	Follow-up	Outcome definition	Outcome diagnostic criteria/instrument	Outcome (%)	Definition of SC use	SC use (%)
Cross-sectional studies								
Depressive symptoms in community samples								
Winstock et al., 2011(b)	Community sample	100 mephedrone users	-	Depressive symptoms	Telephone interview	-	Ever used	100%
Johnson & Johnson 2014	Community sample	110 SC users	-	Depressive symptoms	Online checklist	Decreased appetite (~70%), decreased sex drive (~30%)	Ever used	100%
Ashrafioun et al., 2016	Community sample	104 SC users	-	Depressive symptoms	Online survey	-	Ever used	100%

Study	Design	Participants	Follow-up	Outcome definition	Outcome diagnostic criteria/instrument	Outcome (%)	Definition of SC use	SC use (%)
Jones et al., 2016	Community sample	81 mephedrone users	-	Depressive symptoms	Online survey	-	Last year users	100%
Zimmerman et al., 2019	Community sample	110 SC users	-	Depressive symptoms	Online questionnaire	-	Ever used	100%
Depressive symptoms in selective samples								
Kapitany-Foveny et al., 2020	Clients attending an outpatient drug treatment centre	197 subjects	-	Depressive symptoms	Brief Symptom Inventory	36.1% amongst SC users**	Past year use	22%
Retrospective studies								

Study	Design	Participants	Follow-up	Outcome definition	Outcome diagnostic criteria/instrument	Outcome (%)	Definition of SC use	SC use (%)
Mackay et al., 2011	Case series of SC intoxication	20 cases with mephedrone toxicity	-	Depressive symptoms	Clinical history	20%	Clinical history	100%
Batisse et al., 2014	Case series of SC abuse	21 cases of SC abuse	-	Depressive symptoms	Clinical history	Suicidal ideas (33%) or suicide attempt (10%)	NR	100%
Grapp et al., 2020	Case series of SC intoxication	Nine cases of MDPHP intoxication	-	Depressive symptoms	Clinical history	Suicidal thoughts (11%)	Urine and blood analyses	100%
Schreck et al., 2020	A registry of slammers in France	13 slammers*	-	Depressive symptoms	Clinical history	-	NR	NR

*Only 9 to 13 subjects had depressive symptoms recorded

*Percentage of subjects with prominent symptoms in individual dimensions

Table 8. Findings of studies reporting SC use and depression

Study	Findings	Limitations
Cross-sectional studies		
Depressive symptoms in community samples		
Winstock et al., 2011(b)	The frequencies of depressive symptoms were as follows: tiredness (90%), insomnia (82%), no appetite for food (81%), irritability (64%), and depression (57%).	Selection bias, polydrug use, self-reporting of symptoms, recall bias, no formal assessment of depressive disorder
Johnson & Johnson 2014	Some users reported decreased appetite (~70%) or decreased sex drive (~30%) 'every time' or 'most of the time' SCs were used.	Small sample size, selection bias, uncertain accuracy of responses, no data on the typical SC doses, no formal diagnosis of depression
Ashrafioun et al., 2016	Subjective acute effects of SCs included difficulty sleeping (89%), sadness (18%), decreased sex drive (17%), and decreased energy (7%).	Selection bias, self-reporting of SC use, lack of a non-user control group, recall bias, no formal assessment of depression
Jones et al., 2016	Recovery effects of mephedrone included lack of motivation (92%), irritability (92%), decreased appetite (88%), feeling depressed (87%), and hopelessness (76%).	Selection bias, self-reporting of symptoms, recall bias, no formal assessment of depression
Zimmerman et al., 2019	44.7%, 11.7%, and 3.2% of SC users reported an inability to sleep, suicidal thoughts, and a suicide attempt, respectively, after SC use.	Selection bias, lack of a non-user control group, recall bias, no formal assessment of depression
Depressive symptoms in selective samples		

Study	Findings	Limitations
Kapitany-Foveny et al., 2020	There were no significant differences in the severity of depressive symptoms between SC users and non-SC users.	Retrospective self-reporting of SC use, no clinical diagnosis of depression
Retrospective studies		
Mackay et al., 2011	Depressive symptoms included low mood and suicidality.	Selective sample, small sample size, chart review, polydrug use, no urine or blood analysis, amount of SC use unknown
Batisse et al., 2014	Some patients reported suicidal ideas (33%) or suicide attempts (10%).	Selective sample, small sample size, self-reporting of SC use, no formal diagnosis of depression
Grapp et al., 2020	The prevalence of suicidal thoughts was 11% (1 out of 9).	Selective sample, small sample size, no formal diagnosis of depression
Schreck et al., 2020	The prevalence of sadness, sleep disorders, suicidal ideation, loss of appetite, and weight loss were 56%, 11%, 11%, 11%, and 8%, respectively.	Selective sample, severe cases of slammers were more likely to be reported, small sample size, no formal diagnosis of depression

Anxiety Disorders

The results for anxiety disorders are shown in Tables 9 and 10. Eight cross-sectional studies (n = 3,162) examined the prevalence of anxiety symptoms amongst community-dwelling SC users. The following anxiety symptoms were reported: poor concentration (82%, n = 81), heart racing (74%, 64%–91%, 424 [weighted mean, range, n]), dry mouth (68%, 52%–85%, 214), sweating (67%, 40%–86%, 1,261), anxiousness or restlessness (67%, 50%–79%, 285), body tenseness (60%, n = 104), muscle twitches (59%, n = 104), clenched jaws (52%, n = 110), tremor (51%, 44%–58%, 204), headache (47%, 20%–51%, 1,161), numbness or tingling (47%, n = 104), insomnia (44%, 20%–89%, 418), palpitations (39%, 20%–43%, 1,151), panic (35%, n = 100); ringing in the ears (35%, n = 104), shortness of breath (34%, n = 100), dizziness (24%, 10%–38%, 214), cold limbs (17%, 15%–30%, 1,057), and chest pain (10%, n = 110) (Dargan et al., 2010; Carhart-Harris et al., 2011; Winstock et al., 2011a; Winstock et al., 2011b; Johnson & Johnson 2014; Ashrafioun et al., 2016; Jones et al., 2016; Zimmerman et al., 2019). A cross-sectional study found that 22% of SC users attending an outpatient drug treatment centre had anxiety symptoms (Kapitany-Foveny et al., 2020).

In seven retrospective studies (n = 350), the prevalence of anxiety symptoms was 15% (weighted mean), with a range of 4%–38%. The frequencies of individual anxiety symptoms were as follows: anxiousness (21%, 15%–33%, 272 [weighted mean, range, n]), a rapid heartbeat (15%, n = 13), palpitations (13%, 13%–13%, 238), shortness of breath (10%, 9%–11%, 238), dizziness (8%, n = 149), sweating (8%, n = 13), headache (7%, n = 149), insomnia (4%, 3%–15%, 162), and tremor (3%, 3%–8%, 162) (James et al., 2011; Mackay et al., 2011; Regan et al 2011; Batisse et al., 2014; Beck et al., 2018; Diestelmann et al., 2018; Schreck et al., 2020).

The limitations of the studies discussed above include the use of cross-sectional (Zimmerman et al., 2019) and retrospective designs (Mackay et al 2011); the use of selective samples, such as slammers (Schreck et al., 2020) or drug treatment centre clients (Kapitany-Foveny et al., 2020); a small sample size (Grapp et al., 2020); selection bias (Winstock et al., 2011b); the lack of a control group (Ashrafioun et al., 2016); no data on the SC dose (Johnson & Johnson 2014); polydrug use (Winstock et al., 2011a); no urine or blood analysis (Mackay et al., 2011); variations in the timing of clinical data acquisition and sample collection (Beck et al., 2018); the use anxiety symptoms as an outcome (Zimmerman et al., 2019); under-reporting of symptoms (James et al., 2011); self-reporting of symptoms and hence, uncertain accuracy of the responses (Winstock et al., 2011)); recall bias (Winstock et al., 2011b); and no formal diagnosis of anxiety disorders (Winstock et al., 2011b).

Risk factors

There are no published data on the risk factors for anxiety disorders in SC users.

Neurobiology

There are no published data on the neurobiology of anxiety disorders in SC users.

Clinical course and treatment

There are no published data on the clinical course and treatment of anxiety disorders in SC users.

Table 9. Design of studies reporting SC use and anxiety

Study	Design	Participants	Follow-up	Outcome definition	Outcome diagnostic criteria/instrument	Outcome (%)	Definition of SC use	SC use (%)
Cross-sectional studies								
Anxiety symptoms in community samples								
Dargan et al., 2010	School, college, or university students	1,006 students	-	Anxiety symptoms	Questionnaire	-	Ever used	20.3%
Carhart-Harris et al., 2011	Community sample	1,506 mephedrone users	-	Anxiety symptoms	Web-based survey	NR	Ever used	100%
Winstock et al., 2011(a)	Community sample	947 mephedrone users	-	Anxiety symptoms	Online survey	-	Ever used	100%

Study	Design	Participants	Follow-up	Outcome definition	Outcome diagnostic criteria/instrument	Outcome (%)	Definition of SC use	SC use (%)
Winstock et al., 2011(b)	Community sample	100 mephedrone users	-	Anxiety symptoms	Telephone interview	-	Ever used	100%
Johnson & Johnson 2014	Community sample	110 SC users	-	Anxiety symptoms	Online checklist	-	Ever used	100%
Ashrafioun et al., 2016	Community sample	104 SC users	-	Anxiety symptoms	Online survey	-	Ever used	100%
Jones et al., 2016	Community sample	81 mephedrone users	-	Anxiety symptoms	Online survey	Cannot concentrate (82%), anxiety (79%)	Last year users	100%
Zimmerman et al., 2019	Community sample	110 SC users	-	Anxiety symptoms	Online questionnaire	Rapid heartbeat (63.8%), inability to sleep (44.7%)	Ever used	100%
Anxiety symptoms in selective samples								

Study	Design	Participants	Follow-up	Outcome definition	Outcome diagnostic criteria/instrument	Outcome (%)	Definition of SC use	SC use (%)
Kapitany-Foveny et al., 2020	Clients attending an outpatient drug treatment centre	197 subjects	-	Anxiety symptoms	Brief Symptom Inventory	22.2% amongst SC users**	Past year use	22%
Retrospective studies								
James et al., 2011	Case series of SC toxicity	149 cases of mephedrone toxicity	-	Anxiety symptoms	Clinical history	-	Report by health professionals	100%
Mackay et al., 2011	Case series of SC intoxication	20 cases of mephedrone toxicity	-	Anxiety symptoms	Clinical history	15%	Clinical history	100%

Study	Design	Participants	Follow-up	Outcome definition	Outcome diagnostic criteria/instrument	Outcome (%)	Definition of SC use	SC use (%)
Regan et al., 2011	Case series of SC toxicity	89 cases of mephedrone toxicity	-	Anxiety symptoms	Clinical history	-	Clinical history	100%
Batisse et al., 2014	Case series of SC abuse	21 cases of SC abuse	-	Anxiety symptoms	Clinical history	Anxiety (33%)	NR	100%
Beck et al., 2018	Case series of SC intoxication	Eight cases of pyrovalerone derivative intoxication	-	Anxiety symptoms	Clinical history	38%	Urine and blood analysis	100%
Diestelmann et al., 2018	Case series of recent SC use in a forensic setting	50 cases of recent MDPV use	-	Anxiety symptoms	Clinical history	4%	Urine and blood analyses	100%

Study	Design	Participants	Follow-up	Outcome definition	Outcome diagnostic criteria/instrument	Outcome (%)	Definition of SC use	SC use (%)
Schreck et al., 2020	A registry of slammers in France	13 slammers*	-	Anxiety symptoms	Clinical history	-	NR	NR

NR = not reported

*Only 9 to 13 subjects had anxiety symptoms recorded
**Percentage of subjects with prominent symptoms in individual dimensions

Table 10. Findings of studies reporting SC use and anxiety

Study	Findings	Limitations
Cross-sectional studies		
Anxiety symptoms in community samples		
Dargan et al., 2010	Of the 205 mephedrone users, 42 and 40 reported palpitations and insomnia, respectively.	Selection bias, uncertain accuracy of responses, no formal assessment of anxiety disorders
Carhart-Harris et al., 2011	In the 1,506 users, the most prevalent negative effects were anxiety, panic, and palpitations.	Selection bias, uncertain accuracy of responses, lack of a control group, no formal assessment of anxiety disorders
Winstock et al., 2011(a)	Some users reported excessive sweating (67.2%), headache (50.7%), palpitations (43.4%), or cold fingers or toes (15.3%) after mephedrone use.	Selection bias, high rate of polydrug use, self-reporting of anxiety symptoms, no formal diagnosis of anxiety disorders
Winstock et al., 2011(b)	The frequencies of anxiety symptoms were as follows: sweating (81%), heart racing (74%), restlessness or anxiousness (74%), tremor (58%), anxiety (51%), panic (35%), and shortness of breath (34%).	Selection bias, polydrug use, self-reporting of symptoms, recall bias, no formal assessment of anxiety disorders
Johnson & Johnson 2014	Some users reported heart racing (69%), dry mouth (52%), clenched jaw (52%), excessive sweating (~40%), coldness or numbness in limbs (~30%), headache (~20%), dizziness (~10%), shortness of breath (~10%), tremor (~10%), or chest pain (~10%) 'every time' or 'most of the time' SCs were used.	Small sample size, selection bias, uncertain accuracy of responses, no data on the typical SC doses, no formal diagnosis of anxiety disorders
Ashrafioun et al., 2016	Subjective acute effects of SC included a rapid heartbeat (91%), difficulty sleeping	Selection bias, self-reporting of SC use, lack of a non-user control group, recall

Study	Findings	Limitations
	(89%), increased sweating (86%), dry mouth (85%), body tenseness (60%), muscle twitches (59%), nervousness (50%), numbness or tingling (47%), tremor (44%), headache (40%), dizziness (38%), ringing in the ears (35%), and fear (23%).	bias, no formal assessment of anxiety disorders
Jones et al., 2016	Anxiety was reported by 79% of 81 mephedrone users, and 82% of them reported cannot concentrate.	Recall bias, poly-drug use, self-nomination and self-reporting. Small sample size that might lead to less representative.
Zimmerman et al., 2019	63.8% and 44.7% of subjects reported a rapid heartbeat and an inability to sleep, respectively, after SC use.	Selection bias, lack of a non-user control group, recall bias, no formal assessment of anxiety disorders
Anxiety symptoms in selective samples		
Kapitany-Foveny et al., 2020	Some subjects reported anxiety (8.3%), phobic anxiety (5.6%), and obsession-compulsion (8.3%).	Retrospective self-reporting of SC use, no clinical diagnosis of anxiety disorders
Retrospective studies		
James et al., 2011	Some subjects reported anxiety (15%), palpitations (13%), breathlessness (9%), dizziness (8%), headache (7%), insomnia (3%), and tremor (3%).	Selective sample, indirect measurement and possible under-reporting of anxiety symptoms, no formal diagnosis of anxiety disorders
Mackay et al., 2011	Anxiety symptoms included anxiety and insomnia.	Selective sample, small sample size, chart review, polydrug use, no urine or blood analysis, amount of SC use unknown
Regan et al., 2011	Some subjects reported anxiety or agitation (26%), palpitations (13%), and shortness of breath (11%).	Selective sample, no formal diagnosis of anxiety disorders

Study	Findings	Limitations
Batisse et al., 2014	Some patients reported anxiety (33%).	Selective sample, small sample size, self-reporting of SC use, no formal diagnosis of anxiety
Beck et al., 2018	Anxiety symptoms included panic attacks, anxiety, and palpitations.	Selective sample, small sample size, limited clinical information, timing of clinical data acquisition and sample collection varied, no formal diagnosis of anxiety disorders
Diestelmann et al., 2018	Anxiety symptoms included sweating and panic.	Selective sample, small sample size, no formal diagnosis of anxiety disorders, concurrent use of other substances
Schreck et al., 2020	Some subjects reported anxiety (33%), tachycardia (15%), sleep disorders (11%), sweating (8%), or tremor (8%).	Selective sample, severe cases of slammers were more likely to be reported, small sample size, no formal diagnosis of anxiety disorders

Cognition

Prevalence of cognitive impairment

The cognitive impairment results are shown in Tables 11 and 12. Five cross-sectional studies (n = 505) examined the prevalence of cognitive symptoms amongst community-dwelling SC users. The following cognitive symptoms were reported: loss of memory of the SC session (59%, n = 100); reduced concentration (55%, 25%–82%, 291 [weighted mean, range, n]); enhanced concentration (50%, 50%–50%, 210); memory problems (42%, 23%–63%, 424); and confusion about the time, day, and location (32%, n = 104) (Winstock et al., 2011b; Johnson & Johnson 2014; Ashrafioun et al., 2016; Jones et al 2016; Zimmerman et al., 2019).

Cognitive symptoms were reported in two retrospective studies (n = 59). In one of these studies (n = 50), the prevalence of cognitive symptoms was 34% (Diestelmann et al., 2018). The frequencies of individual cognitive symptoms were as follows: memory problems (5%, 4%–11%, 59 [weighted mean, range, n]), reduced concentration (14%, n = 50), slowed thoughts (14%, n = 50), disorientation (8%, n = 50), and perseverative thinking (25%, n = 50) (Diestelmann et al., 2018; Schreck et al., 2020).

The limitations of the studies discussed above include the use of cross-sectional (Zimmerman et al., 2019) and retrospective designs (Diestelmann et al., 2018); the use of selective samples, such as slammers (Schreck et al., 2020); a small sample size (Schreck et al., 2020); selection bias (Winstock et al., 2011b); the lack of a control group (Ashrafioun et al., 2016); no data on the SC dose (Johnson & Johnson 2014); polydrug use (Winstock et al., 2011a); the use anxiety symptoms as an outcome (Zimmerman et al., 2019); self-reporting of

symptoms and hence, uncertain accuracy of the responses (Winstock et al., 2011b); recall bias (Winstock et al., 2011b); and no formal cognitive assessment (Winstock et al., 2011b).

Impairment of specific cognitive domains

Some studies that compared cognitive function between SC users and non-users have also explored the acute effect of SC use on cognitive function.

Homman et al. (2018) recruited and followed recreational mephedrone users over a period of 9 days. Participants were monitored for mephedrone consumption within the period of testing and those who used mephedrone were compared to those who did not. Forty-six regular mephedrone users participated, with 21 participants voluntarily opting to consume mephedrone 1–3 days after the baseline measurement and 25 opting to abstain. Those who consumed mephedrone reported increased cognitive impairment (Homman et al., 2018).

In a mixed within- and between-subjects design, 20 mephedrone users (regular use for more than 1 year) were compared, first while intoxicated (T1) and second when drug-free (T2). An additional 20 controls were analysed twice when drug-free (T1 and T2). Compared with controls, mephedrone users had generally impaired prose recall ($p = 0.037$). Mephedrone intoxication impaired working memory ($p < 0.001$) and enhanced psychomotor speed ($p = 0.024$) (Freeman et al., 2012).

Herzig et al. (2013) recruited 26 volunteers from the general population who performed tasks to measure verbal learning, verbal fluency, and cognitive flexibility before and after a potential drug-taking situation (pre-clubbing and post-clubbing at dance clubs, respectively). They found that mephedrone users performed worse than non-users at verbal recall and fluency in the pre-clubbing period and the performance deteriorated further from the pre-clubbing to the post-clubbing assessment (Herzig et al., 2013).

In an experiment assessing the effect of mephedrone alone and after co-administration with alcohol on neurocognitive function, 11 participants received single doses of 200 mg of mephedrone or placebo, combined with 0.8 g/kg of alcohol or placebo. Neurocognitive performance was assessed at baseline (T0) and at 1 (T1) and 4 (T2) hours after mephedrone administration. Mephedrone intoxication impaired short-term spatial memory at T1 and improved critical tracking performance at T2. Mephedrone alone did not affect divided attention. These findings support the hypothesis that mephedrone improves psychomotor performance and impairs spatial memory, but does not affect divided attention performance (de Sousa Fernandes Perna et al., 2016).

In summary, mephedrone use impairs certain cognitive functions, namely, verbal and spatial memory and verbal fluency, but enhances psychomotor performance and speed.

Risk factors

There are no published data on the risk factors for cognitive impairment in SC users.

Neurobiology

There are no published data on the neurobiology of cognitive impairment in SC users.

Clinical course and treatment

There are no published data on the clinical course and treatment of cognitive impairment in SC users.

Table 11. Design of studies reporting SC use and cognition

Study	Design	Participants	Follow-up	Outcome definition	Outcome diagnostic criteria/instrument	Outcome (%)	Definition of SC use	SC use (%)
Cross-sectional studies								
Cognitive symptoms in community samples								
Winstock et al., 2011(b)	Community sample	100 mephedrone users	-	Cognitive symptoms	Telephone interview	-	Ever used	100%
Johnson & Johnson 2014	Community sample	110 SC users	-	Cognitive symptoms	Online checklist	More focused than usual (~50%), memory problems (~30%)	Ever used	100%
Ashrafioun et al., 2016	Community sample	104 SC users	-	Cognitive symptoms	Online survey	Difficulty remembering things (56%); confused	Ever used	100%

Study	Design	Participants	Follow-up	Outcome definition	Outcome diagnostic criteria/instrument	Outcome (%)	Definition of SC use	SC use (%)
						about the time, day, and location (32%)		
Jones et al., 2016	Community sample	81 mephedrone users	-	Cognitive symptoms	Online survey	Reduced concentration (82%)	Last year users	100%
Zimmerman et al., 2019	Community sample	110 SC users	-	Cognitive symptoms	Online questionnaire	Trouble concentrating 24.5%), memory loss (23.4%)	Ever used	100%
Retrospective study								
Diestelmann et al., 2018	Case series of recent SC use in a forensic setting	50 cases of recent MDPV use	-	Cognitive symptoms	Clinical history	34%	Urine and blood analyses	100%

Study	Design	Participants	Follow-up	Outcome definition	Outcome diagnostic criteria/instrument	Outcome (%)	Definition of SC use	SC use (%)
Schreck et al., 2020	A registry of slammers in France	Nine slammers*	-	Cognitive symptoms	Clinical history	Amnesia (11%)	NR	NR

*Only 9 subjects had cognitive symptoms reported

Table 12. Findings of studies reporting SC use and cognition

Study	Findings	Limitations
Cross-sectional studies		
Cognitive symptoms in community samples		
Winstock et al., 2011(b)	The frequencies of cognitive symptoms were as follows: forgetting things (63%), unable to concentrate (66%), loss of memory of mephedrone session (59%), and improved concentration during drug use (50%).	Selection bias, polydrug use, self-reporting of symptoms, recall bias, no formal assessment of cognitive disorder
Johnson & Johnson 2014	Some users reported being more focused than usual (~50%) or having memory problems (~30%) 'every time' or 'most of the time' SCs were used.	Small sample size, selection bias, uncertain accuracy of responses, no data on the typical SC doses, no formal assessment of cognitive function
Ashrafioun et al., 2016	Subjective acute effects of SC included difficulty remembering things (56%) and confusion about the time, day, and location (32%)	Selection bias, self-reporting of SC use, lack of a non-user control group, recall bias, no formal assessment of cognitive function
Jones et al., 2016	Recovery effects of mephedrone included reduced concentration (82%).	Selection bias, self-reporting of symptoms, recall bias, no formal assessment of anxiety disorders
Zimmerman et al., 2019	24.5% and 23.4% of subjects reported trouble concentrating and memory loss, respectively, after SC use.	Selection bias, lack of a non-user control group, recall bias, no formal assessment of cognitive function
Retrospective studies		
Diestelmann et al., 2018	Some patients reported cognitive symptoms, such as slowed thoughts (14%), concentration disturbances (14 %), disorientation (8%), memory disturbances (4%),	Selective sample, small sample size, no formal assessment of cognitive function, concurrent use of other substances

Study	Findings	Limitations
	and perseverative thinking (2%).	
Schreck et al., 2020	One subject reported amnesia.	Selective sample, severe cases of slammers were more likely to be reported, small sample size, no formal assessment of cognitive function

SCUD

Prevalence and risk factors

A wide range of SCUD prevalences has been reported amongst SC users in cross-sectional studies, with a weighted mean of approximately 37%. These data strongly support the assertion that SC use, like the use of other substances, such as alcohol, opioids, stimulants, and tobacco, can develop into a use disorder (addiction). A comparison of the conditional prevalence of SCUD with the prevalence of use disorders of other substances can provide additional information with which to gauge the addictive potential of SC. In an online survey report, a similar proportion of dependence was found amongst mephedrone and ecstasy users (Uosukainen et al., 2015). Khat, which contains a naturally occurring cathinone, also has addictive potential. One study assessing the applicability of dependence syndrome, as defined by DSM-IV, found that 31% of a group of 204 khat users of Yemeni origin living in the UK fulfilled the DSM-IV criteria for dependence (Kassim et al., 2013). An Ethiopian study, using the World Health Organization's Composite International Diagnostic Interview, found a lifetime prevalence of khat dependence, according to the ICD-10 criteria, of 5% among male users (1.3% among female users) in a representative sample from a traditional khat-producing area (Awas et al., 1999).

Young users are more likely to have SCUD because young individuals are more likely to use SC due to its relative novelty in the drug market. In a community-based survey of the Ethiopian population, khat chewing was associated with an age between 20–24 years; being uneducated; having a professional, technical, or managerial job; the Muslim religion; being in

the poorest wealth index; being divorced; and having a history of alcohol consumption or cigarette smoking (Akalu et al., 2020). In two studies on pregnant women, khat use was associated with a greater incidence of depressive symptoms and marital distress, alcohol use, and having a partner using khat (Nakajima et al., 2017; Mekuriaw et al., 2020).

Neurobiology

SCs are used as substitutes for other stimulants, such as amphetamines, cocaine, or ecstasy. Pyrrolidine derivatives, such as MDPV, show cocaine-like properties and selectively inhibit dopamine (DAT) and noradrenaline transporters, 10- to 50-fold more potently than cocaine blocks DAT (Baumann et al., 2013a). Some authors found that MDPV has more powerful rewarding and reinforcing effects than cocaine at a tenth of the dose, suggesting that this drug has significant abuse risk, based on its potency and subjective positive effects (Aarde et al., 2013). Repeated administration of psychostimulants induces psychomotor sensitisation in rodents. This phenomenon has been proposed as a model of an initial stage of psychostimulant addiction in humans that contributes to drug craving (Robinson and Berridge, 1993). In a previous study, after twice-daily administration of a moderate dose of MDPV to adolescent mice for 7 days, a significant sensitisation to locomotor effects of cathinone was observed (Duart-Castells et al., 2019). After MDPV treatment, changes in the expression levels of DAT and other proteins persisted longer after withdrawal, indicating a lasting neuroplastic effect similar to the effect of cocaine addiction. However, the implication of the hyperdopaminergic condition in MDPV-induced aggressiveness cannot be ruled out. These neuroadaptive changes and the resulting hyperdopaminergic condition may be involved in the vulnerability to SC addiction (Duart-Castells et al., 2019).

Clinical course and treatment

The course of SCUD is unknown. One study described the nature and time course of a withdrawal syndrome in relation to the cessation of khat use over the first 2 weeks of a quit attempt. Withdrawal symptoms such as depression, craving, nervousness, tiredness, restlessness, poor motivation, irritability, and negative affectivity substantially increased and peaked during the first week, at around day 7, and remained higher than the baseline level, indicating the persistence and severity of these symptoms over time. In addition, craving, irritability, and restlessness significantly reverted to their baseline levels during the second week of the post-quit duration. The rates of success during unaided khat quit attempts were low, with only 7% maintaining abstinence 4 weeks post-quitting (Duresso et al., 2018). Similarly, the remission rate of psychostimulant dependence has also been reported to be low. The remission rate in a 3-year follow-up study of amphetamine dependence (n = 1,016) was 39% (Merinelli-Casey et al., 2007). In four longitudinal studies of subjects with cocaine dependence, the follow-up duration ranged from 4 to 12 years and the remission rate was between 25% and 43% (Calabria et al., 2010).

There are no approved medications for the treatment of SCUD. It has been suggested that the treatment for patients with prolonged exposure to SCs should ideally include a drug management plan coupled with psychotherapy (de Sousa Fernandes Perna et al., 2016). Case reports have suggested that, when treating khat addiction, bromocriptine may be useful in the detoxification procedure. No agent has demonstrated a broad and strong effect at achieving stimulant abstinence (Härtel-Petri et al., 2017; Morley et al., 2017; Buchholz & Saxon 2019). The most promising medications to treat cocaine use disorders are the psychostimulants,

modafinil, bupropion, topiramate, and disulfiram (Buchholz & Saxon 2019). Psychosocial interventions, namely contingency management, have the most evidence for the successful treatment of cocaine and methamphetamine dependence (Roll et al., 2006; Buchholz & Saxon 2019).

Psychosis

Prevalence and risk factors

The prevalence of psychosis amongst SC users in retrospective studies ranges from 9% to 43%, with a weighted mean of 14%. The reported frequencies of psychotic symptoms range from 25% to 80%, with a weighted mean of 35%. In the cross-sectional studies reviewed, 36% of users had paranoia and 20% had hallucinations. Numerous case reports have described khat-induced psychoses as tending to disappear within several days in cases of khat discontinuation and/or after antipsychotic treatment (Manghi et al., 2009). Psychosis is common in stimulant users. In a study of 260 methamphetamine users in Hong Kong, three-quarters of the subjects had lifetime methamphetamine-induced psychotic disorder (MIP). MIP refers to paranoid-hallucinatory states induced by methamphetamine. These states are largely indistinguishable from acute paranoid schizophrenia. A small proportion of the subjects had other psychoses, namely schizophrenia or delusional disorder. MIP was related to more frequent methamphetamine use and higher total consumption in the previous month. Current and lifetime methamphetamine dependence were also associated with MIP, and 91% and 31% of methamphetamine users had lifetime and current psychotic symptoms, respectively (Tang et al., 2020).

In terms of the pattern of psychotic symptoms, 48% of the subjects had transient psychotic symptoms, defined as those that disappeared 1 to 14 days after their last methamphetamine use. Forty-six (18%) subjects had persistent psychotic symptoms (PPS), based on the mean time of 147 days (range, 6–334 days) that had elapsed between their last use of methamphetamine and the day of assessment . One subject had flashbacks. Subjects with psychotic symptoms had higher lifetime consumption of methamphetamine in 1 day, total consumption, total

consumption/body weight, and consumption in 1 day during the past 2 years. Moreover, the group with psychotic symptoms was more likely to have lifetime methamphetamine dependence. With regard to the use of other substances, subjects with psychotic symptoms were more likely to have lifetime use of cannabis and cocaine (Tang et al., 2020).

The exact pathomechanism of SC-induced psychosis is unknown. Similarly, it is not clear why some khat users develop psychosis. However, there are several theories that may explain why psychosis can become chronic and persistent amongst stimulant (methamphetamine) users. Pre-existing schizophrenia may be unmasked or triggered by methamphetamine use; MIP may share a very similar clinical course to that of schizophrenia; or MIP and primary psychosis may not be distinct diagnostic entities, but rather fall along a continuum of psychosis (Glasner-Edwards & Mooney 2014). Indeed, persistent MIP may have similar vulnerability biomarkers to schizophrenia. In a study of exploratory eye movements (EEM), the response search score (a measure of EEM) was lowest in MIP patients with the persistent-type MIP and significantly lower than the scores in those with the transient-type MIP and in healthy controls. However, the response search score did not differ between patients with persistent MIP and those with schizophrenia (Mikami et al., 2003).

Bramness et al. (2012) hypothesised a paradigm of vulnerability to explain the relationship between MIP and psychosis. Under this paradigm, exposure to methamphetamine should be viewed as a stressor in the acute phase for vulnerable individuals. For individuals with lower vulnerability, higher doses of methamphetamine are needed, whereas individuals with higher vulnerability require lower doses to precipitate acute psychosis. In addition, due to its sensitising effects, methamphetamine may play a role in the development of vulnerability to psychosis. Repeated use of methamphetamine could increase vulnerability, thereby increasing the chances of developing psychotic symptoms, even in the absence of acute exposure to methamphetamine.

Neurobiology

The neurobiology of SC- or khat-induced psychosis in unknown. The biological basis for stimulant-induced psychosis includes neurotransmitter dysregulation, oxidative stress and inflammation, genetics, neuroimaging findings, and biomarkers.

The metabolism of methamphetamine works to affect dopamine (DA) transmission in the central nervous system, through the inhibition of the DA transporter and the vesicular monoamine transporter (VMAT2). Inhibition of these proteins results in increased and potentially neurotoxic concentrations of DA. Increased DA concentrations then affect the polysynaptic interactions of different dopaminergic systems (i.e., mesolimbic, nigrostriatal, and mesocortical), resulting in increased glutamate and DA signalling (Bramness et al., 2012). Chronic methamphetamine use subsequently leads to changes in dopaminergic receptor density and function, especially in the mesolimbic system and the striatum, which mediate feed-forward systems, resulting in sensitisation and addiction (Bramness et al., 2012). Excessive DA signalling may overwhelm GABAergic interneurons, leading to the dysregulation of DA systems and possible psychotic symptoms (Hsieh et al., 2014). Damage to cortical interneurons, through impairment of NMDA receptors, and increased neurotoxicity may cause this glutamate dysregulation and result in damage to the cortex, thereby triggering psychotic symptoms (Grant et al., 2012; Hsieh et al., 2014). A limited number of studies have investigated the effects of oxidative stress and inflammation in methamphetamine abuse. However, preliminary studies have demonstrated that both may play a role in the pathology of MIP (Chiang et al., 2019).

Grant et al. (2012) compiled a list of susceptibility genes thought to mediate vulnerability in individuals with a high risk of MIP. Genes were identified based on biological function, differential expression in relevant disease states, their relationship to schizophrenia, and data from animal models. Seven susceptibility genes were selected from over 50 studies conducted in the past two decades (Grant et al., 2012). Of the genes identified, all were related to schizophrenia, four were related to glutamatergic signalling, two to neural development, and one to serotonergic signalling. A study measuring the potential epigenetic dysregulation caused by methamphetamine use observed specific changes in the partial methylation patterns of *LINE-1* in methamphetamine-using subjects (Kalayasiri et al., 2018). Methamphetamine-induced paranoia was strongly associated with changes to a specific partial methylation profile. This study indicates that the dysregulation of *LINE-1* methylation patterns may have a significant effect on both gene expression and the dysregulation of DNA repair genes, thus contributing to the pathophysiology of paranoid psychosis, through neuro-oxidative and immune pathways in these patients.

Neuroimaging studies have found methamphetamine-associated changes in gross structural anatomy, white matter integrity, and metabolism (Chiang et al., 2019). Decreased cortical thickness in brain regions related to affective regulation has been observed in MIP patients, relative to nonpsychotic methamphetamine users and healthy controls (Uhlmann et al., 2016a). Deficits in emotional regulation were associated with reduced cortical thickness in the lateral orbitofrontal cortex, inferior frontal, and temporal gyrus in MIP. Bilateral hippocampal volume was also found to be significantly lower in MIP patients than in methamphetamine users without psychosis. The study noted that all the brain regions mentioned were previously found to be reduced in size in psychotic and schizophrenic populations (Uhlmann et al., 2016b).

MIP patients have been shown to exhibit globally diminished white matter integrity (Breen et al., 2017; Uhlmann et al., 2016a). Uhlmann (2016) et al. observed lower fractional anisotropy in MIP patients than in healthy controls. Moreover, the study found increased mean, axial, and radial diffusivity values in MIP patients, compared with both methamphetamine users without psychosis and healthy controls. Decreases in fractional anisotropy signal a general decrease in white matter integrity, and increased radial and axial diffusivity has been related to decreased myelination and axonal integrity, respectively (Breen et al., 2017). Mean diffusivity has been correlated with the intercellular space and the compactness of white matter, and greater mean diffusivity values were significantly correlated with negative psychotic symptoms in that study (Uhlmann et al., 2016b).

A multimodal brain imaging study showed that methamphetamine users (MIP and nonpsychotic methamphetamine user groups) demonstrated decreased glucose metabolism in the left insula, left precentral gyrus, and the anterior cingulate cortex when compared with healthy controls (Vuletic et al., 2018). Moreover, participants in the MIP group demonstrated decreased glucose metabolism in the left precentral gyrus and left inferior frontal gyrus and both increased glucose metabolism and cerebral perfusion in the putamen and pallidum. The study noted that the increased regional activity of glucose metabolism in the putamen and palladium for the MIP group was consistent with findings from neuroimaging studies of schizophrenia and suggests that the deficits in these regions may be a cause, consequence, or even a compensatory effect of psychosis.

Two functional biomarkers related to ubiquitin-mediated proteolysis downregulation and the upregulation of a circadian clock-related psychoticism have been found to be associated with MIP (Breen et al., 2016). Differential regulation of apolipoprotein C-II (APOC2) and apolipoprotein H (APOH) has been reported in MIP patients when compared with methamphetamine users without psychosis and controls (Breen et al., 2017). Altered

APOH and APOC2 levels have previously been observed in schizophrenia and other psychiatric disorders (Breen et al., 2017). It has been suggested that, apart from lipid metabolism, APOH and APOC2 may be important for the regulation of inflammation and healthy brain functioning (Breen et al., 2017). A machine-learning analysis of 25 blood-related biomarker genes demonstrated that these markers were able to distinguish between MIP patients and methamphetamine dependents with 95% accuracy (Breen et al., 2016).

Clinical course and treatment

The duration of SC-induced psychosis varies from a few hours to several months. Some patients continue to have residual symptoms of psychosis, which can recur following further SC exposure. Case reports suggest that khat-induced psychosis can be transient and self-limiting (Pantelis et al., 1989).

In a study of methamphetamine users in Hong Kong, a fifth of the participants were found to have PPS. PPS was related to higher total consumption of methamphetamine, higher methamphetamine consumption per body weight, methamphetamine consumption on 1 day in the past 2 years and on 1 day in the past 1 year, and lifetime cannabis use (Tang et al., 2020).

Some patients with methamphetamine-induced psychosis recover within 1 week, whereas others do not recover for weeks or months, exhibiting the so-called ‘prolonged type’ of methamphetamine-induced psychosis (Harro 2015). Even if the symptoms abate with abstinence, in 25% to 38% of methamphetamine users, psychosis can re-emerge with repeated use or under stressful situations. If relapse to psychosis follows methamphetamine use, it typically occurs promptly, with 60% of methamphetamine users relapsing within 1 week and 80% relapsing within 1 month (Grant et al., 2012). The identified triggers of recurrence of methamphetamine-induced psychosis include the resumption of methamphetamine use, even

in relatively small amounts, following protracted abstinence; other substance use, including heavy alcohol use; sleep deprivation; and psychosocial stressors (Glasner-Edwards & Mooney 2014). The propensity for methamphetamine use to trigger psychosis in individuals who have previously experienced psychotic symptoms can persist for years, and this phenomenon has been described as 'methamphetamine sensitisation' (Glasner-Edwards & Mooney 2014). Once developed, MIP is predictive of poor outcomes. More than half of the individuals who could follow-up approximately 6 years after the index MIP episode were found to have experienced a relapse of psychosis or had a current alcohol use disorder (Harro 2015).

SC-induced psychosis is commonly treated with benzodiazepam (lorazepam or diazepam) and atypical antipsychotics (quetiapine, olanzapine, risperidone, paliperidone, or aripiprazole). In some patients, antipsychotic treatment is not required, whereas in treatment-resistant cases, electroconvulsive therapy may be required to achieve symptom control. Khat-induced psychosis may also require antipsychotic medications (Pantelis et al., 1989).

Data on the pharmacological treatment of MIP is very limited. Iwanami et al. (1994) examined 104 patients with MIP recruited from a university medical centre and found that all of them were treated with antipsychotic medications. Three studies investigated the efficacy of antipsychotic medications in MIP. In these studies, aripiprazole was more effective than a placebo (Sulaiman et al., 2012); quetiapine and haloperidol were similarly effective (Verachai et al., 2014); and risperidone was more effective for positive symptoms, whereas aripiprazole was more effective for negative symptoms (Farnia et al., 2014).

Studies have demonstrated the benefits of cognitive behavioural therapy (CBT) in the treatment of both psychotic disorders and methamphetamine use disorder. CBT targeting psychosis confers benefits in addition to the effects of antipsychotic medications, particularly in individuals who are resistant to medication. The CBT principles that are used to ameliorate or cope with symptoms associated with other psychotic disorders, such as self-monitoring of

psychotic symptoms, thought challenging, and pleasure predicting, may also be applied to MIP. The use of CBT should be formally studied as a treatment for MIP (Glasner-Edwards & Mooney 2014).

Long-term treatment of MIP should focus on abstinence from methamphetamine, to prevent future episodes of psychosis. Psychosocial treatment in the form of CBT, contingency management, and attendance in 12-step meetings may be considered to reduce methamphetamine use (Glasner-Edwards & Mooney 2014). Psychiatric medications may be prescribed to manage comorbid conditions, such as major depression, anxiety disorders, or persistent psychotic disorders, given that negative affect states, such as depression or anxiety, may increase relapse risk and worsen treatment outcomes in methamphetamine users (Glasner-Edwards & Mooney 2014).

Bipolar disorder

Prevalence and risk factors

The prevalence of mania in SC users is unknown. Common manic symptoms in SC users include increased energy, talkativeness, hyperactivity, fast thoughts, euphoria, excitement, and increased sexual drive. The inability to control laughter and anger or aggressiveness have also been reported. The risk factors for SC-induced mania are not known.

Mania has been reported in khat and stimulant users. Giannini and Castellani (1982) reported a 23-year-old male who displayed symptoms of manic psychosis and increased sympathetic activity following khat ingestion. Rostas and Wolf (2015) described a case of bupropion abuse in a 79-year-old gentleman with a history of alcohol and amphetamine use disorders, resulting in hypomanic symptoms. Conway et al. (2006) reported a case of mania induced by ephedrine ingestion in a woman without prior psychiatric history. Nunes et al. (1989) reported that 30% of 30 cocaine abusers attending a psychiatric clinic had bipolar disorder. Finally, the lifetime prevalence of mania and hypomania was found to be 3.7% and 7.4%, respectively, in 298 hospitalised help-seeking cocaine abusers (Rounsaville et al., 1991). Simulants may induce manic or hypomanic episodes in patients with depressive disorder. Won et al. (2003) reported the induction of a mania episode by fluvoxamine in a 22-year-old single woman with no premorbid depression before using methamphetamine and no genetic vulnerability to depression. In a prospective cohort study including 585 subjects aged 18 to 60 years who had been diagnosed with major depressive disorder, the rate of conversion from major depressive disorder to bipolar disorder in 3 years was 12.4%. The risk of conversion was 3-fold higher in subjects who reported lifetime cocaine use at baseline

relative to individuals who did not report lifetime cocaine use at baseline, after adjusting for demographic and clinical confounders (de Azevedo Cardoso et al., 2020).

Neurobiology

The neurobiology of SC- or khat-induced mania is unknown. Increased dopaminergic neurotransmission has been implicated in the pathophysiology of bipolar disorder (Anand et al., 2000). Stimulants, such as amphetamines, that increase dopamine and norepinephrine release have behavioural effects that resemble mania (Jacobson & Silverstone 1986). In one study, amphetamine challenge led to a significantly greater behavioural response in bipolar patients than in healthy subjects. However, no significant difference was observed in the amphetamine-induced increase in striatal dopamine release between the two groups. Instead, these data are consistent with enhanced postsynaptic dopamine responsivity in patients with bipolar disorder (Anand et al., 2000).

Clinical course and treatment

The clinical course and treatment of bipolar disorder in SC users are yet to be examined. Giannini and Castellani (1982) reported that symptoms in a case of khat-induced mania resolved in 5 hours. Manic symptoms induced by ephedrine (a stimulant) usually cease rapidly following ephedrine withdrawal, but may last for several months in certain patients (Conway et al., 2006). A recent review suggested that substance use disorders have a substantial effect on the diagnosis and management of bipolar disorder. Integrated psychosocial interventions are helpful in decreasing substance abuse. The following medications were evaluated: lithium carbonate, valproate, lamotrigine, topiramate,

naltrexone, acamprosate, disulfiram, quetiapine, and citicoline (Salloum & Brown 2017). The results of three randomised, placebo-controlled studies of dual-diagnosis patients treated with carbamazepine, lithium, and valproate support the use of these agents in dual-diagnosis patients (Vornik & Brown 2006). Another review of psychosocial intervention found that no treatment could consistently alleviate mood symptoms and reduce substance use (Gold et al., 2018).

Depression

Prevalence and risk factors

The prevalence of depressive disorder in SC users is unknown. Common depressive symptoms in SC users include lack of motivation, tiredness, reduced appetite, irritability, hopelessness, insomnia, and depressed mood. Decreased energy, suicidal thoughts, and suicide attempts have also been reported. However, the risk factors for SC-induced depressive disorder are unknown.

Depression has been reported in khat and stimulants users. In a sample of 204 khat chewers, depression and interrupted sleep were reported during khat withdrawal (Kassim et al., 2013). Another study of 59 khat users also found depression, negative affects, tiredness, and poor motivation as part of the withdrawal syndrome (Duresso et al., 2018). In a study of 642 pregnant women, current and former khat users had higher levels of depressive symptoms, compared to non-users (Nakajima et al., 2017). Khat chewing was found to increase the risk of depression by five-fold in a study of 354 university staff (Yeshaw et al., 2017). In a study of 642 undergraduate students, khat use was statistically associated with a higher level of depression symptoms amongst female students (Bahhawi. Et al., 2018). In contrast, in a survey of 800 Yemeni adults, the incidence of adverse depression symptoms was not higher in khat users relative to that in non-users (Numan 2004). Depressive symptoms are also common in methamphetamine users, and they may have fatal consequences. Amongst methamphetamine users, the majority report a lifetime prevalence of depression, and in one study, a third of methamphetamine users had been diagnosed with depression at some point in their lives (Mcketin et al., 2005). The rates of suicidal ideation and attempted suicide are also high in methamphetamine users. Approximately a quarter of

psychostimulant users have a lifetime history of attempted suicide. Higher levels of depression and suicide have been associated with longer methamphetamine use, more frequent use, dependence, and injecting (Darke et al., 2008).

In a sample of 115 Spanish cocaine-dependent users, 24% of the subjects had symptoms scores indicating clinical depression (López et al., 2007). In a group of 25 men in recuperation from substance dependency, the prevalence of depression was found to be 32% (Paiva et al., 2017). In a meta-analysis, depression was shown to be consistently, but modestly, associated with measures of cocaine use amongst cocaine users (Conner et al, 2008). Greater clergy-based support was found to be associated with fewer reported depressive symptoms in a sample of 223 cocaine users (Montgomery et al., 2014).

Neurobiology

The neurobiology of SC- or khat-induced depression is unknown. Depression in methamphetamine abusers may be related to neurochemical abnormalities. Regional brain metabolic and functional changes have also been implicated the pathophysiology of depression. Animal studies indicate that methamphetamine alters dopaminergic, serotonergic, and monoaminergic systems. Post-mortem brain tissue from human methamphetamine users exhibits deficits in striatal dopaminergic markers and in orbitofrontal cortical serotonin. Abstinent methamphetamine users also show a loss of striatal markers for dopamine systems (London et al., 2004). Amongst methamphetamine abusers, self-reports of depressive symptoms have been shown to covary positively with relative glucose metabolism in limbic regions (e.g., perigenual anterior cingulate gyrus and amygdala) (London et al., 2004). An analysis of functional magnetic resonance imaging findings in 19 patients with methamphetamine dependence showed fronto cingulate dysfunction in the Stroop task,

including the left anterior cingulate cortex, paracingulate gyrus, superior frontal gyrus, and frontal pole. These changes were associated with a higher level of depression (Ghavidel et al., 2020).

Clinical course and treatment

The clinical course and treatment of depression in SC users have yet to be examined. In a study of 13 methamphetamine users, depressive symptoms resolved 2 weeks after the cessation of use (Mancino et al., 2011). For the treatment of comorbid depression in stimulant users, quetiapine has been recommended to reduce depressive symptoms in patients with methamphetamine abuse disorders, whereas sertraline should be avoided, as it may increase the drop-out rate. Dietary supplements, such as creatine and citicoline may also be tried (Härtel-Petri et al., 2017). Antidepressants, such as sertraline, mirtazapine, and bupropion, and psychostimulants, such as modafinil and methylphenidate, do not improve depressive symptoms. GABAergic agents or anticonvulsants, such as baclofen and gabapentin, have no effect on depressive symptoms (Härtel-Petri et al., 2017). Psychological approaches, including cognitive behavioural therapy and stepped care, also show no improvement in depressive symptoms (Hellem et al., 2015).

A review of clinical trials supported the use of antidepressant medications for combined cocaine dependence and depression. Most negative studies have evaluated serotonin reuptake inhibitors, whereas positive studies have evaluated agents such as desipramine or bupropion. A substantial number of clinical trials support the efficacy of behavioural treatments for general populations of cocaine abusers and patients with depression, but few studies have addressed the treatment of patients with both disorders

(Rounsaville et al., 2004). For instance, standard contingency management intervention targeting crack cocaine abstinence also leads to significant reductions in depressive symptoms (Miguel et al., 2017).

Anxiety disorders

Prevalence and risk factors

The prevalence of anxiety disorders in SC users is unknown. Common anxiety symptoms in SC users include poor concentration, heart racing, dry mouth, sweating, anxiousness or restlessness, body tenseness, muscle twitches, clenched jaws, tremor, and headache. Numbness or tingling, insomnia, palpitations, panic, ringing in the ears, shortness of breath, dizziness, cold limbs, and chest pain have also been reported. However, the risk factors for SC-induced anxiety disorders are unknown.

Anxiety symptoms have been reported in khat and stimulants users. Khat chewing increased the risk of anxiety by three-fold in a study of 354 university staff (Yeshaw et al., 2017). In a study of 642 undergraduate students, khat use was statistically associated with a higher incidence of anxiety symptoms (Bahhawi. Et al., 2018). In a community sample of 359 subjects, the risk of anxiety was five times higher in khat chewers than in non-chewers (Wondemagegn et al., 2017). In a prospective study of 200 healthy volunteers, there was an increase in mood disturbances in the khat-chewing group, especially shortly after the khat session. This suggests that khat chewing does result in functional mood disorders (Hassan et al., 2002). In contrast, in a survey of 800 Yemeni adults, the incidence of adverse anxiety symptoms was not greater in khat users, compared to non-users (Numan 2004). The frequency of khat use was also not associated with symptoms of anxiety in a sample of 180 Somali men and women (Bhui & Warfa 2010).

The rates of anxiety disorders amongst individuals who use methamphetamine are estimated to be as high as 30.2%. The presence of an anxiety disorder in methamphetamine users is associated with higher rates of relapse, non-adherence to treatment, and poorer

outcomes relative to methamphetamine users without an anxiety disorder (Hellem 2016). Injection drug use has been associated with anxiety symptoms in methamphetamine users (Semple et al., 2011). Anxiety is often a core element of withdrawal symptoms. In a study of 210 methamphetamine-dependent subjects, 34% had anxiety symptoms during acute methamphetamine withdrawal. Female sex, a higher frequency of drug use, and a history of polysubstance use were reported to be significantly correlated with anxiety symptoms during acute methamphetamine withdrawal (Su et al., 2017). In a study of 25 men in recuperation from substance dependency, the prevalence of anxiety was 24% (Paiva et al., 2017), while in another study of 50 cocaine users, it was 10% (Zubaran et al., 2013).

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Neurobiology

The neurobiology of SC- or khat-induced anxiety is unknown. The precise mechanisms by which methamphetamine affects anxiety behaviour is far from being entirely understood. Some studies have indicated that anxious states induced by methamphetamines may be related to increased dopaminergic and glutamatergic transmission. These studies have reported that methamphetamine administration enhances dopamine and glutamate release in several brain regions, such as the prefrontal cortex, striatum, and hippocampus, and leads to the expression of anxiety-like behaviours in rodents. In addition, other studies have reported inflammation as a probable mechanism involved in methamphetamine-induced depression and anxiety (Beirami et al., 2017).

The stress-related neuropeptide corticotropin-releasing factor (CRF) may be linked to anxiety in cocaine users. In laboratory studies, CRF has been implicated in the anxiogenic effects of early cocaine withdrawal. It has been reported that behavioural anxiety, exhibited 48 hours after cocaine withdrawal, is accompanied by a reduction in tissue levels of CRF

immunoreactivity in the amygdala, hypothalamus, and basal forebrain, suggesting increased release of the peptide in these regions. In one study, repeated exposure of animals to cocaine produced changes in the responsivity of the central nervous system to CRF following prolonged drug-free periods, indicating that animals pre-exposed to cocaine may show lasting, potentiated anxiety-like behaviours in response to CRF (Erb et al., 2006).

Clinical course and treatment

The clinical course and treatment of anxiety in SC and khat users have yet to be examined. In a study of 13 methamphetamine users, anxiety symptoms resolved 2 weeks after the cessation of use (Mancino et al., 2011). Anxiety symptoms in methamphetamine users may respond to stimulants, dietary supplements, or exercise. McGaugh et al. (2009) reported that modafinil reduced anxiety symptoms in eight methamphetamine-dependent adults. In a study of 14 methamphetamine-dependent females with comorbid depression, oral creatine monohydrate reduced anxiety symptoms (Hellem et al., 2015). Rawson et al. (2015) found that in 135 methamphetamine-dependent adults, exercise reduced anxiety symptoms. In two small clinical trials, risperidone and mirtazapine were found to be ineffective at reducing anxiety symptoms (Cruickshank et al., 2008; Meredith et al., 2009). In an animal study, cocaine-induced anxiety was alleviated by diazepam, but not by buspirone, dimenhydrinate, or diphenhydramine (Paine et al., 2002).

Cognition

Prevalence and risk factors

Common cognitive symptoms in SC users include memory loss and reduced or enhanced concentration. Disorientation, slowed thoughts, and perseverative thinking have also been reported. Results of laboratory experiments suggest that SC impairs verbal and spatial memory and verbal fluency, but enhances psychomotor performance and speed. However, the risk factors for SC-induced cognitive symptoms are unknown.

Cognitive symptoms have been reported in simulant users. Impaired concentration has been reported in khat users (Al-Morarreb et al., 2002), but the prevalence and risk factors for khat-related cognitive impairment are unknown. Most studies have found that methamphetamine-dependent individuals have lower scores than control subjects on at least some cognitive tests (Dean et al., 2013). On average, the difference in performance between methamphetamine-dependent and control participants tends to be modest, as most significant differences between the groups are within (and often lower than) 1 standard deviation of performance (based on the standard deviations for the groups reported in the studies) (Dean et al., 2013). It has been suggested that approximately 40% of individuals with methamphetamine dependence demonstrate some level of global neuropsychological impairment (Rippeth et al., 2004). Significant deficits in several cognitive processes dependent on brain fronto-striatal and limbic circuits have been observed in studies of chronic methamphetamine users, including deficits in psychomotor functions, complex information processing speed, attention and working memory, episodic memory, and executive functions, including response inhibition and novel problem-solving (Hoffman & Al'Absi 2010). The vast majority of studies have found no relationship between cognitive

performance and the duration of methamphetamine use or estimates of cumulative lifetime dose (Dean et al., 2013). Age, education, and genetics may modulate the relationship between methamphetamine use and cognitive deficits (Dean et al., 2013). Cherner et al. (2010) hypothesised that genetic variability in the metabolism of MA influences neurotoxicity and cognitive function in methamphetamine abusers. Exercise and pharmacological treatment may reduce cognitive symptoms. An aerobic exercise program may have beneficial effects on processing speed in methamphetamine-dependent patients. Modafinil has been shown to improve performance in a test of sustained attention. In addition, in one study, participants with a high baseline frequency of methamphetamine use demonstrated a greater effect of modafinil in tests of inhibitory control and processing speed than those with low baseline use of methamphetamine (Dean et al., 2011). Modafinil may also enhance executive function, memory, and learning (Hester et al., 2010; Ghahremani et al., 2011).

A systematic review of 46 studies revealed moderate impairment across eight cognitive domains during intermediate cocaine abstinence. The most impaired domains were attention, impulsivity, verbal learning and memory, and working memory (Potvin et al., 2014). The potential moderating factors for cognitive impairment in cocaine users include premorbid intelligence, heavy cocaine use, polysubstance use, stress, depression, and insomnia (Mahoney & James 2019). Behavioural treatment addressing these possible moderating factors, such as relapse prevention strategies, sleep hygiene education, and the practice of adaptive coping mechanisms, may alleviate cognitive impairment (Mahoney & James 2019). Psychotropic medications with cognitive-enhancing properties may provide added benefit to improving cognition. Several medications have shown an indication for improving cognitive functioning. Modafinil and rivastigmine have shown some promise in improving cognition in cocaine dependents. Specifically, modafinil, which targets the neurotransmitter dopamine, has been shown to improve performance in measures of working

memory and sustained attention (Kalechstein et al., 2013), whereas rivastigmine, which targets the neurotransmitter acetylcholine, has been shown to improve the span of working memory in individuals with cocaine use disorder (Mahoney et al., 2014).

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Neurobiology

The neurobiology of SC- or khat-induced cognitive impairment is unknown. Neurochemical and structural brain changes may be the underlying mechanisms for the cognitive symptoms observed in methamphetamine and cocaine users. Longitudinal studies of abstinence have shown marked changes in neurochemical markers (i.e., dopamine transporter, glucose metabolism) and grey matter structure in methamphetamine-dependent subjects relative to control subjects who were tested at similar intervals. Some studies have found relationships between changes in the brain and changes in cognitive performance. In a positron emission tomography analysis of methamphetamine-dependent subjects, improvements in neuropsychological performance and increases in dopamine transporter availability showed positive trend relationships (Volkow et al., 2001). In a study of cerebral glucose metabolism, changes in thalamic metabolism were positively correlated with improvements on tests of timed gait, processing speed, and delayed recall (Wang et al., 2004). These findings suggest that changes in the brain during abstinence may be linked to individual differences in cognition. In humans, grey matter alterations in frontal regions have been associated with cognitive function (Hanlon et al., 2011) and decision-making performance (Tanabe et al., 2009). In a study of 29 cocaine users and 38 matched controls, changes in frontal cortical thickness were linked to changes in cognitive performance. The recovery of frontal cortical thickness is accompanied by improved cognitive performance (Hirsiger et al., 2019). In an animal study, cocaine-experienced monkeys required significantly more trials and committed

more errors than control animals in reversal learning and multidimensional discriminations. Cocaine-naive, but not cocaine-experienced, monkeys showed greater metabolic rates of glucose utilisation in the caudate nucleus, hippocampus, anterior and posterior cingulate, and regions associated with attention, error detection, memory, and reward during a multidimensional discrimination task. These data document the direct effects of cocaine self-administration on cognition and neurobiological sequelae underlying the cognitive deficits (Gould et al., 2012). Finally, it has been suggested that cocaine modulates adult hippocampal neurogenesis, which may lead to hippocampal-dependent cognitive symptoms (Castilla-Ortega et al., 2017).

Clinical course and treatment

The clinical course and treatment of cognitive impairment in SC and khat users have yet to be examined. Impairment in some areas of cognitive functioning of methamphetamine-dependent patients may persist into abstinence, be slow to normalise, and may actually worsen initially (Meredith et al., 2005). Methamphetamine-dependent individuals in early abstinence perform markedly worse than controls in measures of attention and psychomotor speed, measures of verbal learning and memory and figural memory, and fluency-based measures of executive function that include set shifting and inhibition (Kalechstein et al., 2003). Verbal memory improves following protracted drug abstinence (Wang et al., 2004). Despite 2–3 months of abstinence, methamphetamine abusers consistently demonstrate errors in selective attention and priming (Salo et al., 2002) and score worse on word recognition tests and tests of episodic memory (Simon et al., 2004). Performance in psychomotor and verbal memory tasks improve after 3–14 months of abstinence, but working memory remains impaired after 6–10 months of abstinence (Chang et al., 2002). A longitudinal study, with a

robust experimental design, that assessed 1 year of abstinence (Iudicello et al., 2010) found that only a certain subset of methamphetamine-dependent individuals improved with abstinence.

A systematic review suggested that in some domains (attention, speed of processing, and verbal learning and memory), impairments are smaller during short-term (urine test still positive) abstinence than during intermediate (≤12 weeks) cocaine abstinence. However, a small degree of impairment is still found after long-term abstinence. These results suggest that some of these deficits may be partially masked by the residual or acute withdrawal effects of cocaine. Cognitive dysfunction remains stable during the first few months of abstinence, but may abate after 5 months of sobriety (Potvin et al., 2014).

Limitations

The limitations of the studies discussed above include the use of a retrospective or cross-sectional design; the use of selective samples; a small sample size; no formal clinical diagnosis; the use of subthreshold symptoms as an outcome; self-reporting or retrospective reporting of SC use; failure to assess the amount, potency, and type of SC used; concurrent use of other drugs; and computerised or Web-based assessment. Data on the risk factors, neurobiology, and course and treatment of SC-related psychiatric disorders are lacking.

Conclusions

Current scientific knowledge strongly supports the contention that SC use can develop into a use disorder (i.e., an addiction). The clinical epidemiology studies reviewed herein indicate that approximately 4 in 10 SC users meet the criteria for a use disorder, with young users more likely to have SCUD. The mean time from the first use of SC to the onset of SCUD, the remission rate, and effective psychosocial interventions or pharmacotherapy approved for the treatment of SCUD remain unknown.

Retrospective studies have shown that amongst SC users, 14% have psychosis and 35% have psychotic symptoms. However, the risk factors and neurobiology of SC-induced psychosis are unknown. The duration of SC-induced psychosis varies from a few hours to several months. Some patients continue to have residual symptoms of psychosis, which can recur following further SC exposure. SC-induced psychosis is commonly treated with benzodiazepam and atypical antipsychotics. In treatment-resistant cases, electroconvulsive therapy may be required to achieve symptom control.

The prevalence of mania, depressive disorder, anxiety disorder, and cognitive impairment in SC users is unknown. Common manic symptoms in SC users include increased energy, talkativeness, hyperactivity, fast thoughts, euphoria, excitement, and increased sexual drive. Common depressive symptoms in SC users include a lack of motivation, tiredness, reduced appetite, irritability, hopelessness, insomnia, and depressed mood. Common anxiety symptoms in SC users include poor concentration, heart racing, dry mouth, sweating, anxiousness or restlessness, body tenseness, muscle twitches, clenched jaws, tremor, and headache. Common cognitive symptoms in SC users include memory loss and reduced or enhanced concentration. Disorientation, slowed thoughts, and perseverative

thinking have also been reported. The results of laboratory experiments suggest that SC impairs verbal and spatial memory and verbal fluency, but enhances psychomotor performance and speed. The risk factors, neurobiology, and clinical course and treatment of bipolar disorder, depression, anxiety, and cognitive impairment in SC users remain unknown.

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