CNS Spectrums

www.cambridge.org/cns

Guidelines

Cite this article: Martinotti G, De Risio L, Vannini C, Schifano F, Pettorruso M, and Di Giannantonio M (2021). Substance-related exogenous psychosis: a postmodern syndrome. *CNS Spectrums* **26**(1), 84–91. https://doi.org/10.1017/S1092852920001479

Received: 12 November 2019
Accepted: 05 May 2020

Key words:
Psychosis; novel psychoactive substances; psychopathology; substance abuse; mental health

Author for correspondence:
Chiara Vannini,
Email: chiaravannini08@gmail.com

© The Author(s), 2020. Published by Cambridge University Press.

CAMBRIDGE UNIVERSITY PRESS

Substance-related exogenous psychosis: a postmodern syndrome

Giovanni Martinotti[1], Luisa De Risio[2], Chiara Vannini[1], Fabrizio Schifano[3], Mauro Pettorruso[1] and Massimo Di Giannantonio[1]

[1]Department of Neuroscience, Imaging, and Clinical Sciences, University "G.d'Annunzio", Chieti-Pescara, Italy, [2]Department of Psychiatry and Addiction, Rome, Italy, and [3]Department of Pharmacy, Pharmacology, and Clinical Sciences, University of Hertfordshire, Hertfordshire, United Kingdom

Abstract

There is growing recognition that substance use is associated with the emergence of psychosis. Elements of post-modernity dominate contemporary social contexts and operate as existential background factors that contribute to the emergence of substance-related psychotic phenomena, particularly use of potent and highly rewarding novel psychoactive substances (NPS). About 25% of first-episode psychoses are substance-induced (SIP). DSM-5 SIP diagnosis is based on the assumption that symptoms are transient and disappear after sustained abstinence. This narrowed definition does not consider the issue of persistent SIP. There is a clear need for a new diagnostic framework that provides reliable, unambiguous clinical criteria to differentiate between comorbid conditions (i.e., schizophrenia patients with a substance use disorder) and substance-related psychoses. In the present contribution, we aim to outline a novel and separate clinical entity: substancerelated exogenous psychosis (SREP). Within this diagnostic category, we refer to both transientand persistent psychoses associated with substance use. SREP is conceived as a distinct psychoticdisorder with psychopathological specificities that clearly differentiate it from schizophrenia. We address differences in terms of clinical presentation, epidemiology, etiological models and treatment response. SREP is characterized by altered states of consciousness, persecutory delusions, visual and cenesthetic hallucinations, impulsivity and psychomotor agitation, affectiveand negative symptoms, a pervasive feeling of unreality and intact insight. Delusions are typically secondary to abnormal perception resulting from a characteristic "sensorialization" of the world. Longitudinal studies are warranted to substantiate our hypothesis of a novel diagnostic categoryand support the clinical validity of SREP. This may have important implications in terms of early differential diagnosis and staging (i.e., between comorbid conditions, persistent and transientsubstance-related psychotic states) as well as choice of treatment interventions.

Postmodern Society and Psychopathology

The past two decades have been marked by dramatic social changes, widely characterized by the term "postmodern." These major transformations have had profound and complex implications for psychiatry, influencing mental health risk factors, dynamics in clinical encounters, styles of help-seeking behavior, and clinical outcomes. Underlying themes of postmodern thought that are particularly relevant to psychiatry include individualization and social roles, the nature of self-identity and intimacy, and future orientation.[1]

A defining element of postmodernity, also driven by the massive spread of signification through the Internet, is an absolute reliance on the present to the exclusion or proportional reduction of the past and future. As first described by Edmund Husserl[2] and Bin Kimura[3] with the notion of the *presentatio* or *intrafaestum* modality, the present is disconnected from preoccupations with the future and the past (including feelings of guilt). Contemporary adolescents and young adults are restricted to instantaneity, with loss of the ability to wait. The sociologist Oriel Sullivan's notion of "*speed-up society*" echoes this general acceleration of temporal patterns[4] (ie, increase in "time intensity" and feelings of "time pressure"). For instance, Rosa[5] describes acting at a faster rhythm throughout the day, getting rid of pauses or intervals between our actions, and increased multitasking. In theoretical analyses of postmodern social acceleration and popularizations of the idea of the "*speed-up society*,"[6–8] the increasing tempo of daily life is considered central to social change. Many recent accounts of temporal acceleration are directly related to the effect of Technology (Information and Communication Technology [ICT]). There have been huge changes in ICT over the past decade, and this is reflected in a growing acceleration of interconnectivity, digitalization, and gaming technologies, with major effects on perceptions of time pressure.

The paradigm of *liquid society*, first introduced by Zygmunt Bauman,[9] underscores constant change, discontinuity, and lack of structure in modern social life; doubt and perplexity are the only stable elements. A flame is an effective metaphorical image of this condition: an open system that constantly works to maintain an equilibrium, never evolving in an organized temporal structure. Meares[10] argues that the existential situation of these subjects is dominated by point-events that never meet. Existence is "held hostage" by an eternal present, absorbed into immediacy, resulting in feelings of unreality and sometimes heightened excitement, anger, and impulsivity. In postmodern adolescents/young adults, these emotional states are accompanied by dysphoric mood. In this context, psychoactive substances act as powerful catalysts, enhancing this atemporal rewarding experience.

Substance Use Disorders: The New Scenario

Licit and illicit psychoactive substances are cheap and easily available to the postmodern adolescent. They allow for rapid and effortless adjustments of consciousness and emotional states to the ever-changing present. Substance use disorders (SUDs) are a major health concern: in 2010, SUDs were among the leading causes of years lived with disability worldwide.[11] Currently, substance use is so widespread that it can be hardly defined as an aberrant behavior, although consequences are dramatic in terms of mortality and psychiatric load. As discussed by Devereux,[12] every society has its own norms and rules, providing the individual with different possible ways of conveying both illness/distress and success/fulfillment. In postmodern society, substance use is connected to both scenarios. Stimulants are often thought to support successful lifestyles, "empowering" and enhancing the narcissistic invulnerability that permeates certain personality structures. On the other hand, substance use typically has the effect of producing an experience of wholeness, which excludes complexity and heterogeneity in favor of the security of a single experience, thus dampening psychological distress and offsetting feelings of inadequacy and fragmentation of the self in vulnerable subjects who have difficulty coping with "speed-up." In this view, SUDs and associated psychopathology are a sort of culture-bound syndrome, profoundly rooted in the fundamentals of liquid postmodernity.

In addition to "traditional" psychoactive substances, novel psychoactive substances (NPS) are raising increasing international concern, especially in relation to the fast-moving and potentially limitless nature of their online market.[13–18] NPS have been legally defined by the European Union (EU) as new narcotic or psychotropic drugs, in pure form or preparation, that are not scheduled under the Single Convention on Narcotic Drugs of 1961 or the Convention on Psychotropic Substances of 1971, but pose a public health threat potentially comparable to substances listed in those conventions (Council of the EU decision 2005/387/JHA).[19] In 2017, the total number of NPS in the EU was over 670, of which 632 were notified after 2004 (EMCDDA, 2018). NPS are often unknown to health professionals, mainly due to lack of evidence-based sources of information.[20] Internet (ie, online forums, chat rooms, and blogs) has emerged as a primary source of information on drugs in general and NPS in particular. An estimated 61% of young Europeans aged 15 to 24 typically quote the Internet as a source of information on drugs.[21] Users share their experiences with different substances and recommend sources and routes of delivery. Vulnerable young consumers are targeted by aggressive marketing strategies (ie, attractive names, colorful packaging, and free samples to test), increasing the likelihood of early exposure to substances. NPS are mostly unregulated, and this may increase their popularity as well as the flawed perception of low risks associated with use. Unfortunately, to date, few surveys on NPS diffusion have been conducted. Furthermore, there is increasing evidence that NPS use is often unintentional.[22] Growing evidence supports the potential serious psychiatric and physical consequences related to NPS consumption.[17,23] Originally, the most common NPS were phenethylamines and tryptamines. In recent years, cathinones, synthetic cannabinoids (SCs), phencyclidine (PCP), and benzofurans have gained increasing popularity.[24] A number of NPS have been directly or indirectly associated with serious adverse effects and fatalities: 2-DPMP and D2PM, two synthetic stimulants belonging to the class of piperidines, have shown both neuropsychiatric and cardiovascular toxicity, and have been involved in three deaths in August 2010.[25] Misuse of gamma-hydroxybutyrate and gamma-butyrolactone has been implicated in more than 150 fatalities in the United Kingdom from 1995 to 2013[26] and, more recently, stimulant mixtures and SCs have emerged as potentially life-threatening.[16] Moreover, the use of novel synthetic opioids (NSOs) is another relevant issue, with an increasing number of deaths in the United States and Canada due to overdose.

NPS use is widespread among adolescents/young adults and frequent among psychiatric patients reporting psychotic symptoms at disease onset. Also, there is substantial evidence that NPS are a major risk factor for violence and aggression in patients with major mental disorders.[27–30]

Substance-Related Psychoses

Substance use often co-occurs with schizophrenia and other psychiatric disorders. Rates of SUD among psychiatric patients are significantly higher than in the general population (up to 50%).[31] High levels of comorbidity add to the diagnostic difficulties faced by clinicians and researchers in accurately differentiating substance-induced psychopathology from primary psychiatric disorders in the context of co-occurring SUDs. According to the Diagnostic and Statistical Manual of Mental Disorders–5 (DSM-5), between 7% and 25% of first-episode psychosis subjects have a substance-induced psychosis (SIP).[32] In a Norwegian sample, the incidence of SIP was approximately 6.5 in 100,000 persons per year, compared to 9.7 with a primary psychotic disorder (PPD) and comorbid substance use, and 24.1 with PPD alone. Although patients with SIP use substances at higher rates than patients with PPD, substance use is in fact still pervasive among patients with PPD, with reported rates varying from 35% to 61%. Subjects with chronic and heavy substance use (cannabis, amphetamines, psychedelics, and cocaine) are at highest risk.[33] There is a growing recognition that substance use is associated with the emergence of psychosis, which develops during the use of the substance, and may or may not subside following withdrawal or abstinence. Subjects with SIP often call the police or ambulance and present in emergency rooms because they or family/friends feel a need for urgent intervention. Substance use, often heavy and long-term, suddenly transforms the subject's perception and/or cognition into frightening experiences that are not recognized as due to acute intoxication and require an urgent response. Some subjects may have been experiencing substance-induced psychotic phenomena for months before the symptoms motivate help-seeking. Despite this, surprisingly little research has focused on differentiating SIP from

https://doi.org/10.1017/S1092852920001479 Published online by Cambridge University Press

	SIP		SREP
	DSM-5	ICD-X	
Core definition	Psychotic symptoms arise soon after substance intoxication/withdrawal, and do not occur exclusively during delirium		
Onset (in relation to substance use)		Immediately after (<48 h)	
Remission	Within 1 month	Within 6 months	Possible persistence
Delusion/ Hallucinations	Prominent	Present	Possibly present
Insight	Absent		Usually intact
Negative symptoms			Pronounced
Atypical features*			Present
Experience of time			Presentification, hyperstability

***Atypical features:** affective symptoms, impulsiveness, violent behavior*

Figure 1. SIP and SREP: clinical and psychopathological characteristics. Abbreviations: DSM-5, Diagnostic and Statistical Manual of Mental Disorders–5; ICD-10, International Classification of Diseases–10; SIP, substance-induced psychosis; SREP, substance-related exogenous psychosis.

PPD with substance use, especially with regard to determining whether these disorders have different trajectories and outcomes.[34]

Little is known about potential factors associated specifically with SIP, and the adequacy of current classification systems in appropriately distinguishing between primary and substance-induced disorders is questionable.[35,36] The phenomenon of substances causing transient psychotic states was first mentioned in studies from the 1960s,[37] with several experimental studies demonstrating drug effects mimicking the positive (eg, hallucinations, delusions, paranoia, and disorganized thinking) and negative (eg, affective flattening, anhedonia, and attentional and cognitive impairment) symptoms of schizophrenia.[35] Current major neurobiological theories of schizophrenia have their origin in the effects of substances: the effects of lysergic acid diethylamide (LSD) gave rise to the serotonergic model, amphetamines to the dopamine (DA) hypothesis, PCP and ketamine to the glutamatergic model and, more recently, the effects of cannabis have provoked interest in the role of endocannabinoids. Numerous substances are linked to the development of psychosis, and diagnoses of SIP have been included in both the International Classification of Diseases–10 (ICD-10) (World Health Organization) and the DSM-5.[32,39] The fourth edition of the DSM first introduced the term SIP in 1994. In the DSM-5, the diagnostic criteria for SIP remain essentially unchanged. SIP is defined as a condition in which psychotic symptoms (hallucinations and/or delusions) arise during or soon after substance intoxication/withdrawal and resolve within a set time period. Psychotic symptoms cannot occur exclusively during the course of a delirium. According to the DSM-5, symptoms should be more severe than those expected to occur with intoxication or withdrawal, and they should warrant the need for health care. There should be a lack of insight into hallucinations and delusions, and symptoms should resolve within the somewhat loosely defined timeframe of "about a month."[32] Interestingly, this definition does not consider negative symptoms, probably excluding a relevant area of clinical manifestations. ICD-10 has a slightly different and more stringent time criterion in that it requires partial resolution within 1 month and full resolution of symptoms within 6 months (Figure 1). In clinical practice, distinguishing between SIP and PPD with concurrent substance use remains a diagnostic difficulty.[39] Misdiagnoses have major implications in terms of clinical management resulting in suboptimal follow-up and inappropriate treatment, with a potentially poorer prognosis.[35] In the DSM, a diagnosis of SIP is based on the assumption that symptoms are transient and disappear after sustained abstinence (Figure 1). Literature suggests that diagnostic change over time is common: rate of change from SIP to PPD ranges from 25% to 50%,[40,41] as are high rates of transition to mood disorders. A recent meta-analysis reports that SIP is associated with a substantial risk for transition to schizophrenia, particularly following cannabis-induced psychosis.[42] High transition rates are partly related to progression of the psychotic disorder (ie, SIP develops into PPD), and partly a result of the narrowed definition of SIP that may favor misdiagnosis (ie, SIP diagnosed as Schizophreniform Disorder or Psychosis NOS when criteria for schizophrenia are not fulfilled).[35] Neither the ICD-10 nor the DSM-5 allows for coding of "persistent states" of SIP, in spite of growing literature suggesting that in some chronic users psychotic symptoms can last substantially longer than the indicated timeframes.[42,44] The diagnosis should then be changed from SIP to PPD. But even then, the question of whether chronic substance use induces a long-lasting, clinically distinct psychotic syndrome or whether it precipitates a PPD (ie, schizophrenia) remains unanswered. The problem of differential diagnosis has hampered research on the specific psychopathology and the prospective outcomes of individuals with psychoses following substance use.[45] These psychotic disorders may be a separate diagnostic entity from PPD that is stable over time and has distinctive psychopathological features.

In the present contribution, we aim to outline a novel and separate clinical entity, which we describe as substance-related exogenous psychosis (SREP). As previously stated, the narrowed

https://doi.org/10.1017/S1092852920001479 Published online by Cambridge University Press

definition of SIP does not consider the issue of persistent psychoses that are clinically distinct from PPD. Within this novel diagnostic category, we refer to both transient and persistent forms of psychoses induced by substances (ie, with onset following substance use). SREP can be considered a schizophrenia spectrum disorder but displays specific characteristics that clearly differentiate it from Schizophrenia/PPD, in terms of clinical presentation, epidemiology, etiological models, and treatment response.

SREP: Epidemiology and Etiopathological Models

Epidemiology

Epidemiological data regarding prevalence and distribution of SREP have highlighted relevant differences compared to primary psychoses. In 2013, the American Psychiatric Association reported that prevalence rates of schizophrenia were similar around the world,[32] with higher incidence rates in racial/ethnic minorities and in urban areas with lower levels of owner-occupied housing, and in subjects using high-potency cannabis daily, as recently showed by the EU-GEI group.[46,47] SREP typically emerges in the modern and developed world and has been mostly described in urban areas with high population density and rapid economic growth, where substance use represents a possible way to cope with "social acceleration" and high levels of environmental stressors.[48] Our hypothesis is that the higher incidence rates in some areas is a result of the presence of SREP cases erroneously classified as schizophrenia. However, we should also consider that substance misuse is still pervasive among patients with schizophrenia, with reported rates varying from 35% to 61%. Clear diagnostic criteria, currently not available, and longitudinal studies are required to clarify the role of SREP in terms of prevalence.

Etiopathological models

Significant differences have also been hypothesized from a psychopathological perspective.

Phenomenologically oriented researchers propose that a disturbance of the basic self is a phenotypic trait marker of psychotic vulnerability.[49] This hypothesis is based on a combination of empirical research and philosophical considerations. The type of self-disturbance proposed as being a core abnormality in schizophrenia concerns the pre-reflective level of selfhood (ipseity). Self-disorders become progressively more articulated and thematized as psychotic symptoms develop, crystallizing in the form of delusions, hallucinations, and passivity phenomena. When substance use becomes a relevant factor in the development of a psychotic experience, this model needs to be integrated by a wider perspective. As previously discussed, a substantial number of substance users (especially if use is continuous and heavy) present persistent psychotic symptoms, opening questions regarding substance use and the development of a full, atypical chronic psychosis. In this context, the hexogen model of psychosis and its toxic subtype, defined lysergic psychoma, may be helpful in the understanding of substance-induced phenomena. The term "lysergic psychoma" was first used by Cargnello and Callieri in 1963, though it has its roots in Hellpach's definition and in Karl Bonhoeffer's hexogen model.[50] It describes a syndrome characterized by a clear egodystonic experience in which the subject perceives the presence of a "foreign body" in his mind. The thinking Ego can feel and observe it as an uncommon experience, out of control, enriched by hallucinations (mainly visual and kinesthetic), delusional perceptions and, in some cases, structured but confined delusional thoughts. The Ego is still aware and "in charge," and usually tries to suppress the psychoma. This experience is usually transient and self-limiting, strictly connected to the pharmacodynamic effects exerted by the substance. However, repeated and heavy exposure as well as the long-lasting pharmacokinetic properties of some NPS opens up a possible new scenario. When the thinking Ego has to face a recurring and intense abnormal experience (ie, unusual thoughts or perceptions), its resilience weakens and its capacity to contain the experience fails. If the psychoma becomes stable, the capacity to offset it is progressively reduced and it invades the functioning part of the Ego. The lysergic psychoma is an exogenous clinical expression that almost all substance users experience, regardless of the substance type. Clearly, the pharmacodynamics of the drug taken is responsible for the specificity of the induced phenomena. The dopaminergic psychoma is most frequently reported as long-lasting and has the worst prognosis, as described for shaboo and methamphetamine users in southeastern Asia. Methamphetamine-induced psychosis[51] is, in fact, a severe form of paranoid schizophrenia, in which the psychoma has become fully pervasive.[51]

SREP: Clinical and Psychopathological Characteristics

In terms of clinical presentation, SREP exhibits specific features (Figure 1). Descriptive studies found specific clinical characteristics that distinguish psychoses associated with substance use from schizophrenia and that may drive differential diagnosis. Caton et al identified key demographic, family, and clinical differences between SIP and PPD in 400 participants with at least one psychotic symptom, use of alcohol and/or other drugs in the previous 30 days, and no psychiatric inpatient history in the previous 6 months.[52] Patients with SIP had more visual hallucinations, a higher prevalence of suicidal thoughts during the previous year, more violent behavior, family history of substance use, and higher levels of insight.[33] Other systematic studies aiming to characterize SIP as defined by DSM-5 and persistent, atypical psychotic disorders associated with substance use (ie, SREP) are lacking, and descriptions are mostly anecdotal. We briefly discuss possible distinctive clinical and psychopathological features associated with SREP (Figure 1), as reported in existing descriptive studies.

The intersection between drug intoxication and psychosis is an altered state of consciousness, with a dramatic reduction in the field of consciousness (twilight state or crepuscular consciousness). The field of consciousness is restricted to a few or even a single content. Depersonalization and derealization are typical and reversible experiences that characterize the twilight state. The latter is often also accompanied by illusions and hallucinosis and may represent a transitory state between the transient substance-induced psychotic experience and a full-blown, persistent psychosis. Psychosis emerging from crepuscular consciousness is marked by cognitive alterations, perceptual and thought disorders, and affective symptoms. When normal consciousness is restored (ie, the field of consciousness widens again), it sometimes opens up to new meaning in the context of a transformed, delusional reality experience. Both quantitative and qualitative alterations of consciousness should be routinely assessed in patients with a probable alcohol/substance use. These alterations are unusual in psychiatric disorders, with the exception of dissociative disorders, frequently described in literature as substance-induced symptoms[53] and may help guide early differential diagnosis.

https://doi.org/10.1017/S1092852920001479 Published online by Cambridge University Press

Modification of affectivity accompanied by depersonalization and derealization has been widely described.[54,55] Several studies report affective symptoms (eg, depressed mood, self-neglect, and hostility) and suicidal ideation.[56–58] Affective symptoms are possibly a core clinical feature of SREP and are not recognized in current diagnostic criteria.[59]

Delusions, mostly persecutory/paranoid, are usually secondary to abnormal perception resulting from a characteristic "sensorialization" of the world and of experience.[55, 60] Messas observed these features in a population of crack users in San Paolo (Brazil) and described several fundamental elements of these psychoses, partly related to cultural and social postmodern determinants: (1) hyperstability, a form of existence based on the experience of the present, cut off from the past and future; (2) freezing of the sense of time, with inability to wait and invest in the future; (3) hyper-materiality, where the sense of space and time are condensed in the present experience; and (4) nonevolving, crystallized delusions, which remain condensed inside the experience of present time. These psychopathological correlates emphasize the role of substances as mediators of social drifts. These delusional experiences are unstable, in a rapid-changing on-off state, and insight is fluctuating.

Typically, intact insight has been reported as a common feature among patients with SREP.[55,61,62] DSM-5 criteria consider hallucinations/delusions as symptoms of SIP only when they occur in the absence of insight and suggest that a substance user with hallucinations/delusions and insight into these should be coded as having "perceptual disturbances." However, patients with SREP appear more likely to interpret symptoms as a result of substance use compared to PPD patients.

Hallucinations and other perception disorders are frequently reported in SREP. Visual and cenesthetic hallucinations are more common. This is probably related to the potent interaction exerted on the 5HT receptors by modern hallucinogens, like MDMA and other similar compounds. In SREP, perceptual alterations probably pave the way to thought disorders. Drastic substance-induced changes of the perception-movement cycle may influence judgment. Therefore, substance-induced delusions are not primary, but secondary to intense changes and distortions of perception. Substance-induced delusions are characterized by confirmation and interpretation, not by revelation, and by fantastic contents. In line with the lysergic psychoma model, SREP delusions are similar to paraphrenic delusions, with a feeling of unreality, while the ability to analyze the feeling is preserved.[62]

Aggressiveness appears to be transnosographic, probably representing an intrinsic element correlated with substance use. Patients with SREP generally have high levels of impulsivity and often display violent behavior and severe psychomotor agitation (eg, bizarre/disorganized behavior and motor hyperactivity).[52] Polysubstance use has also demonstrated a strong correlation with aggression in emergency departments, together with higher risks of unprotected sex, car accidents, violence, and victimization.[63] Positive urine drug screen results for cannabis have been associated to a higher incidence of inpatient agitation among patients admitted to a psychiatric inpatient unit with a diagnosis of schizophrenia, schizoaffective disorder, or bipolar disorder.[64]

SREP: Pharmacological Models of Clinical Presentation

SREP can be differentiated into specific syndromes, associated with the use of different compounds. Substances may precipitate the imbalance of a wide range of neurotransmitters, pathways, and receptors: DA (mostly associated with psychedelic phenethylamines/synthetic cathinones), CB-1R activation (synthetic cannabimimetics), 5-HT2A receptor activation (tryptamine derivatives/hallucinogenic plants), antagonist activities at both NMDA and mGlu2/3 receptors (PCP-like derivatives), and k opioid receptor activation (*Salvia divinorum*).

Substances mainly acting on dopaminergic pathways are primarily associated with paranoid thoughts and auditory hallucinations. Delusions of reference, persecution, grandeur, and jealousy, as well as hypomanic states, are frequently reported. Aggressiveness and irritability are common, often with dysphoria, anxiety, and panic episodes. With mephedrone, low mood, loss of appetite, difficulty sleeping, paranoid ideation, cognitive impairment, changes in perception, agitation, hallucinations, amnesia, confusion, violence, and suicidal thoughts have been reported.[65–69] Users also reported positive effects (eg, euphoria, improved psychomotor speed, alertness, and talkativeness).[70–72] Cathinone-induced acute intoxication may include symptoms of the serotonin syndrome, such as aggression and hyperthermia, psychotic symptoms, catatonia, and hyperactive delirium.[73–80] Mood disturbances and paranoid ideation have been observed in chronic users of cathinones. Rasmon Kalayasiri's study[81] reports that up to 40% of individuals who use methamphetamine may experience psychotic symptoms or paranoia.

In line with their pharmacological profile, molecules that have high serotonin/DA ratios are similar to entactogenic substances, such as MDMA. Conversely, high DA/serotonin ratios predict a strong stimulant experience. Furthermore, high or low affinity to noradrenergic systems may be associated with varying sympathetic nervous system activation, whereas activation of 5-HT2A/1A receptors is likely to predict hallucinogenic effects.[82]

Substances acting predominantly on serotonergic pathways are most commonly implicated in the development of visual hallucinations with vivid colors, frequently associated with intense positive or negative emotional experiences. Hallucinogens are also called "psychedelics" (eg, LSD and psilocybin), "psychotomimetics" (as their effects mimic psychotic symptoms), and "entheogens" (due to the mystical-type experiences these drugs may induce). Hallucinogens may induce hallucinations, illusions, and "pseudo-hallucinations" (hallucinations the patient recognizes as not resulting from external stimuli), as well as intense emotional responses.[83] In order of frequency, the other possible disordered perceptions are kinesthetic and tactile. The presence of auditory, olfactory, and gustatory hallucinations is uncommon. Paranoid delusions, particularly with religious content, are possible, but full-blown systematic delusions are rare. Hypomanic states are frequently reported, although suicidal thoughts and depressive states may also occur. The predominant clinical effects of tryptamines include visual hallucinations, alterations in sensory perception, distortion of body image, depersonalization, marked mood lability, and anxiety/panic.

Substances mainly acting on glutamatergic pathways usually determine dissociative reactions, such as derealization and somatopsychic depersonalization. Visual abnormal perception may be reported, mainly in the form of distortions and illusions. Bodily and kinesthetic hallucinations are frequent, as is the occurrence of near-death experiences. Auditory, olfactory, and gustatory hallucinations are less common. Delusions with somatic themes are frequent: Ekbow, Capgras, and Cotard syndromes have been reported, as well as episodes of demoniac possession and vexation. Negative symptoms are common. Mood is mainly flat, accompanied by

https://doi.org/10.1017/S1092852920001479 Published online by Cambridge University Press

affective blunting, anhedonia, and a general sense of anesthesia and detachment from the surrounding environment. Irritability and aggressiveness may be noted. The "K-hole" is an out-of-body/near-death experience, with the user becoming trapped in a state of detachment from physical presence. Residual symptoms, such as flashbacks and perceptual distortions, may follow.

Cannabis intoxication is associated with anxiety and transient psychosis-like or psychotomimetic effects that include depersonalization, derealization, psychomotor agitation, disorganized behavior, ideas of reference, grandiose and paranoid delusions, flight of ideas, disorganized thinking, and auditory and visual hallucinations. Such effects have been increasingly reported with high THC-containing strains of cannabis and SCs ("spice," "K2," and "kush"), generally CB1R and CB2R full agonists. Literature describes cases of new-onset psychosis named "Mojo Psychosis" following the intake of SC mixtures.[84]

While low doses of SCs produce similar psychoactive effects to cannabis/THC, higher doses often lead to auditory/visual hallucinations, anxiety, and intense feelings of paranoia.[85,86] Other psychiatric and neurological effects include behavioral dyscontrol and agitation[87]; mood swings [88]; suicidal ideation and suicide attempts; panic attacks; thought disorganization; and hyperactive delirium.[89] A florid/acute transient psychosis, relapse/worsening of a pre-existing psychosis or bipolar disorder,[90,91] and persistent psychotic disorder/"Spiceophrenia"[83,92] have all been described. Intoxication/acute toxic effects of SCs appear to be more akin to those experienced with sympathomimetic/stimulant drug use.[93,94] It is interesting to note that some SCs exhibit pharmacologically relevant affinity for psychosis-associated receptors, including D2, 5-HT2A, and NMDA. Skryabin et al[95] highlighted four clinical variants of SC-induced psychoses: (1) psychosis with predominant delirium symptoms, (2) psychosis with predominant hallucinatory symptoms, (3) psychosis with predominant affective-delusional symptoms, and (4) psychosis with predominant mental automatism.

Substances acting on the opiate system do not usually determine clear psychotic syndromes. NSOs toxicity includes drowsiness, sedation, disorientation, slurred speech, confusion, dizziness, nausea, miosis, slowed breathing, and respiratory depression.[96] Conversely, NSOs psychotropic effects include anxiolysis, euphoria, feeling of relaxation, and mood lift, dysphoric, and dissociating effects.[97] Other compounds classified among NSOs are desomorphine ("krokodil"), mitragynine and 7-hydroxymitragynine (alkaloids found in "kratom"/*Mitragyna speciose*),[98] and salvinorin A, with its analogue herkinorin, which are the main components of *Salvia divinorum*. Salvinorin A's psychoactive effects include perceptual disturbances, psychosis, irritability, and anxiety.

A range of experiences may be associated with use of high doses of gabapentinoids, including euphoria, improved sociability, opiate-like sedation, entactogenic feelings/dissociation, and psychedelic effects.[83]

These phenomena (serotonergic, dopaminergic, and glutamatergic psychoma) cannot be considered as different syndromes, given the frequent overlap of symptoms. This is due to the fact that some NPS exert their effect on different pathways, and that the occurrence of polyabuse is the norm rather than the exception. However, the ability to differentiate and characterize clinical presentation may be useful to plan an appropriate therapeutic approach.

Conclusion

There is a clear need for a new diagnostic framework that provides reliable, unambiguous clinical criteria to differentiate between comorbid conditions (ie, schizophrenia patients with SUD) and clinically distinct psychoses associated with substance use, given that 1/3 of individuals with SIP develop a severe mental illness, schizophrenia spectrum disorders, or bipolar disorders, within 2 to 3 years.[33,99] Moreover, psychotic phenomena following substance use in patients with a primary diagnosis of mood disorder or borderline personality disorder need to be recognized and clearly distinguished from other forms of psychoses, with relevant consequences in terms of treatment. Also, early differential diagnosis and staging between persistent psychoses associated with substance use (ie, SREP) and transient psychotic states occurring during substance intoxication/withdrawal is necessary.

In this paper, we address these issues and make a first attempt to bridge this gap by discussing current literature on psychoses associated with substance use and proposing a new clinical and diagnostic entity, SREP. SREP is conceived as a distinct psychotic disorder with psychopathological specificities that develops following mostly chronic substance use and persists well beyond use. This distinction may have important implications for choice of treatment interventions (ie, the contentious issue of long-term antipsychotic medication in substance-related phenomena). Potent and highly rewarding NPS are frequently associated with SREP and will likely challenge and shape substance-related psychopathology for years to come. SREP is highly represented in our postmodern *liquid society*, marked by instantaneity and rapid transformation, where substance use is often an adaptive trait. Elements of postmodernity (ie, instability of self-identity) dominate contemporary social contexts and possibly operate as existential background conditions that contribute to the emergence of psychotic phenomena following substance use. Longitudinal studies are needed in order to confirm our hypothesis giving strength and clinical validity to the diagnostic category of SREP.

Disclosure. The authors ensure the absence of conflict of interest.

References

1. Whitley R. Postmodernity and mental health. *Harv Rev Psychiatry*. 2008; **16**:352–364.
2. Husserl E. *Ideas Pertaining to a Pure Phenomenology and to a Phenomenological Philosophy*. Dordrecht, The Netherlands: Kluwer; 1982.
3. Kimura B. *Scritti di Psicopatologia e Fenomenologia*. Roma, Italy: Giovanni Fioriti; 2005.
4. Sullivan O, Gershuny J. Speed-up society? Evidence from the UK 2000 and 2015 time use diary surveys. *Sociology*. 2017;**52**:20–38.
5. Rosa H. *Social Acceleration: A New Theory of Modernity*. New York, NY: Columbia University Press; 2013.
6. Colvile R. *The Great Acceleration: How the World Is Getting Faster, Faster*. New York, NY: Bloomsbury; 2016.
7. Crary J. *24/7: Late Capitalism and the Ends of Sleep*. London, UK: Verso Books; 2013.
8. Schulte B. *Overwhelmed: Work, Love and Play When No-One Has the Time*. New York, NY: Sarah Crichton Books; 2014.
9. Bauman Z. *Liquid Modernity*. Cambridge, UK: Polity Press; 1999.
10. Meares R. The sense of the spirit as a form of conversation. *Asian J Psychiatr*. 2012;**5**:190–192.
11. Whiteford HA, Ferrari AJ, Degenhardt L, Feigin V, Vos T. The global burden of mental, neurological and substance use disorders: an analysis from the Global Burden of Disease Study 2010. *PLoS One*. 2015;**10**: e0116820.
12. Devereux G. Normale e anormale. In: Devereux G, ed. *Saggi di etnopsichiatria generale*. Roma, Italy: Armando Editore; 1956:23–93.
13. Cinosi E, Martinotti G, Simonato P, *et al*. Following "the Roots" of Kratom (*Mitragyna Speciosa*): the evolution of an Enhancer from a traditional use to increase work and productivity in Southeast Asia to a recreational

https://doi.org/10.1017/S1092852920001479 Published online by Cambridge University Press

psychoactive drug in Western countries. *Biomed Res Int*. 2015;**2015**. doi: 10.1155/2015/968786.
14. Schifano F, Leoni M, Martinotti G, Rawaf S, Rovetto F. Importance of cyberspace for the assessment of the drug abuse market: preliminary results from the Psychonaut 2002 project. *Cyberpsychol Behav*. 2003;**6**(4):405–410.
15. Schifano F, Deluca P, Agosti L, *et al.* New trends in the cyber and street market of recreational drugs? The case of 2C-T-7 ("Blue Mystic"). *J Psychopharmacol*. 2005;**19**(6):675–679.
16. Santacroce R, Corazza O, Martinotti G, Bersani FS, Valeriani G, Di Giannantonio M. Psyclones: a roller coaster of life? Hidden synthetic cannabinoids and stimulants in apparently harmless products. *Hum Psychopharmacol*. 2015;**30**(4):265–271. doi:10.1002/hup.2410.
17. Martinotti G, Di Nicola M, Quattrone D, *et al.* Novel psychoactive substances and induced phenomena in psychopathology: the lysergic psychoma. *J Psychopathology*. 2015;**21**:400–405.
18. Corazza O, Valeriani G, Bersani FS, Corkery J, Martinotti G, Bersani G, *et al.* "Spice," "Kryptonite," "Black Mamba": an overview of brand names and marketing strategies of novel psychoactive substances on the Web. *J Psychoactive Drugs*. 2014;**46**(4):287–294. doi:10.1080/02791072.2014.944291.
19. Council of the European Union decision 2005/387/JHA United Nations Office on Drugs and Crime (UNODC), World Drug Report, United Nations Publication, Sales.
20. Corazza O, Assi S, Simonato P, *et al.* Promoting innovation and excellence to face the rapid diffusion of novel psychoactive substances in the EU: the outcomes of the ReDNet project. *Hum Psychopharmacol*. 2013;**28**:317–323.
21. Eurobarometer. Young people and drugs: analytical report. http://ec.europa.eu/public opinion/flash/fl 233 en.pdf. 2009.
22. Salomone A, Palamar JJ, Gerace E, Di Corcia D, Vincenti M. Hair testing for drugs of abuse and new psychoactive substances in a high-risk population. *Anal Toxicol*. 2017;**41**(5):376–381. doi:10.1093/jat/bkx020.
23. Simonato P, Corazza O, Santonastaso P, *et al.* Novel psychoactive substances as a novel challenge for health professionals: results from an Italian survey. *Hum Psychopharmacol*. 2013;**28**(4):324–331. doi: 10.1002/hup.2300.
24. European Monitoring Centre for Drugs and Drug Addiction-EMCDDA, Annual Report 2015.
25. Corkery JM, Elliott S, Schifano F, Corazza O, Ghodse AH. 2-DPMP (desoxypipradrol, 2-benzhydrylpiperidine, 2-phenylmethylpiperidine) and D2PM (diphenyl-2-pyrrolidin-2-yl-methanol, diphenylprolinol): a preliminary review. *Prog Neuropsychopharmacol Biol Psychiatry*. 2012;**39**(2):253–258.
26. Corkery JM, Loi B, Claridge H, *et al.* Gamma hydroxybutyrate (GHB), gamma butyrolactone (GBL) and 1,4-butanediol (1,4-BD; BDO): a literature review with a focus on UK fatalities related to non-medical use. *Neurosci Biobehav Rev*. 2015;**53**:52–78.
27. Soyka M. Substance misuse, psychiatric disorder and violent and disturbed behaviour. *Br J Psychiatry*. 2000;**176**:345–350.
28. Fazel S, Smith EN, Chang Z, Geddes JR. Risk factors for interpersonal violence: an umbrella review of meta-analyses. *Br J Psychiatry*. 2018;**213**(4):609–614.
29. Shafi A, Gallagher P, Stewart N, Martinotti G, Corazza O. The risk of violence associated with novel psychoactive substance misuse in patients presenting to acute mental health services. *Hum Psychopharmacol*. 2017;**32**:
30. Martinotti G, Cinosi E, Santacroce R, *et al.* Substance-related psychopathology and aggressiveness in a nightlife holiday resort: results from a pilot study in a psychiatric inpatient unit in Ibiza. *Hum Psychopharmacol*. 2017;**32**:e2586. https://doi.org/10.1002/hup.25866
31. Jablensky A, McGrath J, Herrman H, *et al.* Psychotic disorders in urban areas: an overview of the Study on Low Prevalence Disorders. *Aust N Z J Psychiatry*. 2000;**34**(2):221–236.
32. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th edition. Arlington, VA: American Psychiatric Publishing; 2013.
33. Beckmann D, Lowman KL, Nargiso J, McKowen J, Watt L, Yule AM. Substance-induced psychosis in youth. *Child Adolesc Psychiatr Clin N Am*. 2020;**29**(1):131–143. doi:10.1016/j.chc.2019.08.006.
34. Weibell MA, Hegelstad V, Johannessen JO. Substance-induced psychosis: conceptual and diagnostic challenges in clinical practice. In: Preedy VR, ed. *Neuropathology of Drug Addictions and Substance Misuse*. Cambridge, MA: Academic Press; 2016.
35. Mathias S, Lubman DI, Hides L. Substance-induced psychosis: a diagnostic conundrum. *J Clin Psychiatry*. 2008;**69**(3):358–367.
36. Rounsaville BJ. DSM-V research agenda: substance abuse/psychosis comorbidity. *Schizophr Bull*. 2007;**33**(4):947–952.
37. Angrist BM, Gershon S. The phenomenology of experimentally induced amphetamine psychosis—preliminary observations. *Biol Psychiatry*. 1970;**2**(2):95–107.
38. World Health Organization (WHO). *The ICD-10 Classification of Mental and Behavioural Disorders*. 1992.
39. Schanzer BM, First MB, Dominguez B, Hasin DS, Caton CL. Diagnosing psychotic disorders in the emergency department in the context of substance use. *Psychiatr Serv*. 2006;**57**(10):1468–1473.
40. Caton CL, Hasin DS, Shrout PE, *et al.* Stability of early-phase primary psychotic disorders with concurrent substance use and substance-induced psychosis. *Br J Psychiatry*. 2007;**190**:105–111.
41. Crebbin K, Mitford E, Paxton R, Turkington D. First-episode drug-induced psychosis: a medium term follow up study reveals a high-risk group. *Soc Psychiatry Psychiatr Epidemiol*. 2009;**44**(9):710–715.
42. Murrie B, Lappin J, Large M, Sara G. Transition of substance-induced, brief, and atypical psychoses to schizophrenia: a systematic review and meta-analysis. *Schizophr Bull*. 2020;**46**:505–516.
43. Weibell MA, Hegelstad WTV, Auestad B, *et al.* The effect of substance use on 10-year outcome in first-episode psychosis. *Schizophr Bull*. 2017;**43**:843–851.
44. Weibell MA, Johannessen JO, Auestad B, *et al.* Early substance use cessation improves cognition-10 years outcome in first-episode psychosis patients. *Front Psychiatry*. 2019;**10**:–495.
45. Wilson L, Szigeti A, Kearney A, Clarke M. Clinical characteristics of primary psychotic disorders with concurrent substance abuse and substance-induced psychotic disorders: a systematic review. *Schizophr Res*. 2018;**197**:78–86.
46. Hannah E, Jongsma MPH, Gayer-Anderson C, *et al.* Treated incidence of psychotic disorders in the multinational EU-GEI study. *JAMA Psychiatry*. 2018;**75**:36–46.
47. Di Forti M, Quattrone D, Freeman TP, *et al.* The contribution of cannabis use to variation in the incidence of psychotic disorder across Europe (EU-GEI): a multicentre case-control study. *Lancet Psychiatry*. 2019;**6**:427–436.
48. Kienast T, Stoffers J, Bermpohl F, Lieb K. Borderline personality disorder and comorbid addiction: epidemiology and treatment. *Dtsch Arztebl Int*. 2014;**111**:280–286.
49. Sass LA, Parnas J. Schizophrenia, consciousness, and the self. *Schizophrenia Bulletin*. 2003;**29**(3):427–444.
50. Bonhoeffer K. Die exogenen Reaktionstypen. *Archiv f. Psychiatrie*. 1917;**58**:58–70.
51. Wearne TA, Cornish JL. A comparison of methamphetamine-induced psychosis and schizophrenia: a review of positive, negative, and cognitive symptomatology. *Front Psychiatry*. 2018;**9**:491.
52. Caton CL, Drake RE, Hasin DS, *et al.* Differences between early-phase primary psychotic disorders with concurrent substance use and substance-induced psychoses. *Arch Gen Psychiatry*. 2005;**62**:137–145.
53. Vik PW, Cellucci T, Jarchow A, Hedt J. Cognitive impairment in substance abuse. *Psychiatr Clin North Am*. 2004;**27**(1):97–109.
54. Messas G, Tamelini M, Mancini M, Stanghellini G. New perspectives in phenomenological psychopathology: its use in psychiatric treatment. *Front Psychiatry*. 2018;**9**:466.
55. Di Petta G. *Le Psicosi Sintetiche*. Giovanni Fioriti Editore; 2016.
56. Akiyama K, Saito A, Shimoda K. Chronic methamphetamine psychosis after long-term abstinence in Japanese incarcerated patients. *Am J Addict*. 2011;**20**(3):240–249.
57. Fraser S, Hides L, Philips L, Proctor D, Lubman DI. Differentiating first episode substance induced and primary psychotic disorders with concurrent substance use in young people. *Schizophr Res*. 2012;**136**(1–3):110–115.
58. Hides L, Dawe S, McKetin R, *et al.* Primary and substance-induced psychotic disorders in methamphetamine users. *Psychiatry Res*. 2015;**226**(1):91–96.

https://doi.org/10.1017/S1092852920001479 Published online by Cambridge University Press

59. Voce A, Burns R, Castle D, Calabria B, McKetin R. Is there a discrete negative symptom syndrome in people who use methamphetamine? *Compr Psychiatry*. 2019;**93**:27–32.
60. Messas G. The association between substance use/abuse and psychosis: a phenomenological viewpoint. 2015–2016. Messas, Guilherme. Comprendre 25-26.
61. Matsumoto T, Kamijo A, Miyakawa T, *et al.* Methamphetamine in Japan: the consequences of methamphetamine abuse as a function of route of administration. *Addiction*. 2002;**97**(7):809–817.
62. Martinotti G, Lupi M, Carlucci L, *et al.* Novel psychoactive substances: use and knowledge among adolescents and young adults in urban and rural areas. *Hum Psychopharmacol*. 2015;**30**(4):295–301.
63. Goldstick JE, Stoddard SA, Carter PM, Zimmerman MA, Walton MA, Cunningham RM. Characteristic substance misuse profiles among youth entering an urban emergency department: neighborhood correlates and behavioral comorbidities. *Am J Drug Alcohol Abuse*. 2016;**42**(6):671–681.
64. Johnson JM, Wu CY, Winder GS, Casher MI, Marshall VD, Bostwick JR. The effects of cannabis on inpatient agitation, aggression, and length of stay. *J Dual Diagn*. 2016;**12**(3–4):244–251.
65. Homman L, Seglert J, Morgan MJ. An observational study on the sub-acute effects of mephedrone on mood, cognition, sleep and physical problems in regular mephedrone users. *Psychopharmacology*. 2018;**235**(9):2609–2618. doi:10.1007/s00213-018-4953-1.
66. Sullivan S, Herzig D, Mohr C, *et al.* Theory of mind and social functioning in first episode psychosis. *Cogn Neuropsychiatry*. 2013;**18**(3):219–242.
67. Kehr J, Ichinose F, Yoshitake S, *et al.* Mephedrone, compared with MDMA (ecstasy) and amphetamine, rapidly increases both dopamine and 5-HT levels in nucleus accumbens of awake rats. *Br J Pharmacol*. 2011;**164**(8):1949–1958.
68. Capriola M. Synthetic cathinone abuse. *Clin Pharmacol*. 2013;**5**:109–115. doi:10.2147/CPAA.S42832.
69. Lovrecic B, Lovrecic M, Gabrovec B, *et al.* Non-medical use of novel synthetic opioids: a new challenge to public health. *Int J Environ Res Public Health*. 2019;**16**(2):177. doi:10.3390/ijerph16020177.
70. Deruiter WK, Cheng C, Gehrs M, Langley J, Dewa CS. Substance abuse and smoking among a Canadian cohort of first episode psychosis patients. *Community Ment Health J*. 2013;**49**(6):815–821.
71. Dargan PI, Albert S, Wood DM. Mephedrone use and associated adverse effects in school and college/university students before the UK legislation change. *QJM*. 2010;**103**(11):875–879. doi:10.1093/qjmed/hcq134.
72. Mdege ND, Meader N, Lloyd C, Parrott S, McCambridge J. In: NIHR Journals Library, ed. *The Novel Psychoactive Substances in the UK Project: Empirical And Conceptual Review Work To Produce Research Recommendations*. Southampton, UK; 2017.
73. Warrick BJ, Hill M, Hekman K, *et al.* A 9-state analysis of designer stimulant, "bath salt," hospital visits reported to poison control centers. *Ann Emerg Med*. 2013;**62**(3):244–251. doi:10.1016/j.annemergmed.2012.12.017.
74. Mugele J, Nañagas KA, Tormoehlen LM. Serotonin syndrome associated with MDPV use: a case report. *Ann Emerg Med*. 2012;**60**(1):100–102.
75. Hohmann N, Mikus G, Czock D. Effects and risks associated with novel psychoactive substances: mislabeling and sale as bath salts, spice, and research chemicals. *Dtsch Arztebl Int*. 2014;**111**(9):139–147.
76. Turner J, Mitchell JL, Carroll BT, Denysenko L. Dextromethorphan/quinidine withdrawal-emergent catatonia. *Ann Clin Psychiatry*. 2016;**28**(2):138–139.
77. Otahbachi M, Cevik C, Bagdure S, Nugent K. Excited delirium, restraints, and unexpected death: a review of pathogenesis. *Am J Forensic Med Pathol*. 2010;**31**:107–112.
78. Penders TM, Gestring R. Hallucinatory delirium following use of MDPV: "Bath Salts". *Gen Hosp Psychiatry*. 2011;**33**(5):525–526.
79. Weaver MF. Prescription sedative misuse and abuse. *Yale J Biol Med*. 2015;**88**(3):247–256.
80. Penders TM, Gestring RE, Vilensky DA. Intoxication delirium following use of synthetic cathinone derivatives. *Am J Drug Alcohol Abuse*. 2012;**38**:616–617.
81. Kalayasiri R, Kraijak K, Maes M, Mutirangura A. Methamphetamine (MA) use induces specific changes in LINE-1 partial methylation patterns, which are associated with MA-induced paranoia: a multivariate and neuronal network study. *Mol Neurobiol*. 2019;**56**:4258–4272.
82. Baumeister D, Tojo LM, Tracy DK. Legal highs: staying on top of the flood of novel psychoactive substances. *Ther Adv Psychopharmacol*. 2015;**5**(2):97–132.
83. Schifano F, Papanti GD, Orsolini L, Corkery JM. Novel psychoactive substances: the pharmacology of stimulants and hallucinogens. *Expert Rev Clin Pharmacol*. 2016;**9**(7):943–954.
84. Orsolini L, Chiappini S, Papanti D, De Berardis D, Corkery JM, Schifano F. The bridge between classical and "synthetic"/chemical psychoses: towards a clinical, psychopathological, and therapeutic perspective. *Front Psychiatry*. 2019;**10**:851.
85. Bonaccorso S, Metastasio A, Ricciardi A, *et al.* Synthetic cannabinoid use in a case series of patients with psychosis presenting to acute psychiatric settings: clinical presentation and management issues. *Brain Sci*. 2018;**8**(7):133
86. Winstock AR, Barratt MJ. The 12-month prevalence and nature of adverse experiences resulting in emergency medical presentations associated with the use of synthetic cannabinoid products. *Hum Psychopharmacol*. 2013;**28**:390–393.
87. Brakoulias V. Products containing synthetic cannabinoids and psychosis. *Aust N Z J Psychiatry*. 2012;**46**(3):281–282. doi:10.1177/0004867411433974.
88. Celofiga A, Koprivsek J, Klavz J. Use of synthetic cannabinoids in patients with psychotic disorders: case series. *J Dual Diagn*. 2014;**10**(3):168–173.
89. Schifano F, Orsolini L, Papanti D, Corkery J. NPS: medical consequences associated with their intake. *Curr Top Behav Neurosci*. 2017;**32**:351–380.
90. Oluwabusi OO, Lobach L, Akhtar U, Youngman B, Ambrosini PJ. Synthetic cannabinoid-induced psychosis: two adolescent cases. *J Child Adolesc Psychopharmacol*. 2012;**22**(5):393–395.
91. Ustundag MF, Ozhan Ibis E, Yucel A, Ozcan H. Synthetic cannabis-induced mania. *Case Rep Psychiatry*. 2015;**2015**:
92. Papanti D, Schifano F, Botteon G, *et al.* "Spiceophrenia": a systematic overview of "spice"-related psychopathological issues and a case report. *Hum Psychopharmacol*. 2013;**28**(4):379–389.
93. Wood DM, Dargan PI. Novel psychoactive substances: how to understand the acute toxicity associated with the use of these substances. *Ther Drug Monit*. 2012;**34**(4):363–367.
94. Naviglio S, Papanti D, Moressa V, Ventura A. An adolescent with an altered state of mind. *BMJ*. 2015;**350**:h299.
95. Skryabin VY, Vinnikova M, Nenastieva A, Alekseyuk V. Hallucinogen persisting perception disorder: a literature review and three case reports. *J Addict Dis*. 2019;**37**:268–278.
96. Suzuki J, El-Haddad S. A review: fentanyl and non-pharmaceutical fentanyls. *Drug Alcohol Depend*. 2017;**171**:107–116. doi:10.1016/j.drugalcdep.2016.11.033.
97. Solimini R, Pichini S, Pacifici R, Busardò FP, Giorgetti R. Pharmacotoxicology of non-fentanyl derived new synthetic opioids. *Front Pharmacol*. 2018;**9**:654. doi:10.3389/fphar.2018.00654.
98. Rech MA, Donahey E, Cappiello Dziedzic JM, Oh L, Greenhalgh E. New drugs of abuse. *Pharmacotherapy*. 2014;**35**(2):189–197.
99. Schifano F, Napolitano F, Chiappini S, *et al.* New/emerging psychoactive substances and associated psychopathological consequences. *Psychol Med*. 2019. doi: 10.1017/S0033291719001727

https://doi.org/10.1017/S1092852920001479 Published online by Cambridge University Press