

## Substance Related Exogenous Psychosis: a post-modern syndrome

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### Post-modern 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; future orientation (Whitley r. 2008)  
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A defining element of post-modernity, 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<sup>2</sup> and Bin Kimura<sup>3</sup> 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<sup>4</sup> (i.e., increase in “time intensity”, feelings of “time pressure”). For instance, Rosa<sup>5</sup> (2013) describes: acting at a faster rhythm throughout the day; getting rid of pauses or intervals between our actions; increased multitasking. In theoretical analyses of post-modern social acceleration and popularizations of the idea of the ‘*speed-up society*’<sup>6,7,8</sup>(e.g. Colvile, 2016; Crary, 2013; Schulte, 2014), 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<sup>9</sup>, 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<sup>10</sup> 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, impulsivity. In post-modern adolescents/young adults, these emotional states are accompanied by dysphoric mood. In this context, psychoactive substances act as powerful catalysts, enhancing this a-temporal rewarding experience.

### **Substance Use Disorders: the new scenario**

Licit and illicit psychoactive substances are cheap and easily-available to the post-modern adolescent, allowing 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 [Whiteford, L. Degenhardt, 2015]<sup>11</sup>. 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<sup>12</sup>, every society has its own norms and rules, providing the individual with different possible ways of conveying both illness/distress and success/fulfillment. In post-modern 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, that 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 post-modernity.

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 (Cinosi et al., 2015; Schifano, Leoni, Martinotti, Rawaf & Rovetto, 2003; Schifano et al., 2005; Santacroce, Corazza, Martinotti, Bersani, Valeriani & Di Giannantonio, 2015; Martinotti et al., 2015a; Corazza et al., 2014)<sup>13,14,15,16,17,18</sup>. 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) [United Nations Office on Drugs and Crime (UNODC), World Drug Report, United Nations Publication, Sales]<sup>19</sup>. 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 (O. Corazza, S. Assi et al., 2013)<sup>20</sup>. Internet (i.e., online forums, chat rooms, blogs) has emerged as a primary source of information on drugs in general and NPS in particular. An estimated 61% of young Europeans aged 15-24 years typically quote the Internet as a source of information on drugs [Eurobarometer, Young people and drugs: analytical report, 2009, [http://ec.europa.eu/public\\_opinion/flash/fl\\_233\\_en.pdf](http://ec.europa.eu/public_opinion/flash/fl_233_en.pdf)]<sup>21</sup>. Users share their experiences with different substances, and recommend sources and routes of delivery. Vulnerable young consumers are targeted by aggressive marketing strategies (i.e., attractive names, colorful packaging, 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 (Salomone, Palamar, et al 2017)<sup>22</sup>. Growing evidence supports the potential serious psychiatric and physical consequences related to NPS consumption<sup>23, 17</sup> (Simonato et al., 2013; Martinotti et al., 2015a). Originally, the most common NPS were phenethylamines and tryptamines. In recent years cathinones, synthetic cannabinoids (Spice), phencyclidine and benzofurans have gained increasing popularity (EMCDDA, Annual Report 2015)<sup>24</sup>. 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<sup>25</sup> (Corkery, Elliott, Schifano, et al. 2012). Misuse of gamma-hydroxybutyrate (GHB) and gamma-butyrolactone (GBL) has been implicated in more than 150 fatalities in the UK from 1995 to 2013<sup>26</sup> (Corkery JM, Loi B, et al., 2015) and, more recently, stimulant mixtures and synthetic cannabinoids have emerged as potentially life-threatening<sup>27</sup> (Santacroce et al., 2015). Moreover, the use of novel synthetic opioids is another relevant issue, with an increasing number of deaths in the US 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<sup>28,29,30, 31</sup> [Soyka, 2000; Fazel et al. 2018; Shafi A et al. 2017; Martinotti G., Cinosi E, et al 2017].

### **Substance-Related Psychoses**

Substance use often co-occurs with schizophrenia and other psychiatric disorders. Rates of substance use disorder (SUD) among psychiatric patients are significantly higher than in the general population (up to 50%) (Jablensky et al. 2000)<sup>32</sup>. 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 SUD. According to the DSM-5, between 7% and 25% of first-episode psychosis subjects have a Substance-induced Psychosis (SIP) (American Psychiatric Association, 2013). Subjects with chronic and heavy substance use (cannabis, amphetamines, psychedelics, cocaine) are at highest risk. 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. SIP subjects 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 primary psychotic disorders (PP) with substance use, especially with regards to determining whether these disorders have different trajectories and outcomes (Weibell, Hegelstad, and Johannessen 2016)<sup>33</sup>. 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 (Mathias, Lubman, and Hides 2008; Rounsaville 2007)<sup>34,35</sup>. The phenomenon of substances causing transient psychotic states was first mentioned in studies from the 1960s (Angrist and Gershon 1970)<sup>36</sup>, with several experimental studies demonstrating drug effects mimicking the positive (e.g., hallucinations, delusions, paranoia and disorganized thinking) and negative (e.g., affective flattening, anhedonia, attentional and cognitive impairment) symptoms of schizophrenia<sup>34</sup>. 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 hypothesis; phencyclidine (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 (WHO) 1992) and the Diagnostic and Statistical Manual of Mental Disorders 5 (DSM-5) (American Psychiatric Association. 2013)<sup>37,38</sup>. The fourth edition of the DSM first introduced the term SIP in 1994. In the DSM-5, the diagnostic criteria for SIP essentially remain 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” (American Psychiatric Association. 2013). 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. In clinical practice, distinguishing between SIP and PP with concurrent substance use remains a diagnostic difficulty <sup>39</sup>(Schanzer et al. 2006). Misdiagnoses have major implications in terms of clinical management resulting in suboptimal follow-up and inappropriate treatment, with a potentially poorer prognosis (Mathias et al., 2008) <sup>40</sup>. In the DSM, a diagnosis of SIP is based on the assumption that symptoms are transient and disappear after sustained abstinence. Literature suggests that diagnostic change over time is common: rate of change from SIP to PP ranges from 25% to 50% (Caton et al. 2007; Crebbin et al. 2009) <sup>41,42</sup>. A recent meta-analysis reports that SIP is associated with a substantial risk for transition to schizophrenia, particularly following cannabis-induced psychosis (Murrie et al. 2019) <sup>43</sup>. High transition rates are partly related to progression of the psychotic disorder (i.e., SIP develops into PP), and partly a result of the narrowed definition of SIP that may favor misdiagnosis (i.e., SIP diagnosed as Schizophreniform Disorder or Psychosis NOS when criteria for schizophrenia are not fulfilled) (Mathias, Lubman, and Hides 2008) <sup>40</sup>. Neither the ICD-10 nor the DSM-V allow 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 (Weibell, Hegelstad, et al, 2017; Weibell, Johannessen et al 2019). <sup>44,45</sup> The diagnosis should then be changed from SIP to PP. But even then, the question of whether chronic substance use induces a long-lasting, clinically distinct psychotic syndrome or whether it precipitates a primary psychotic disorder (i.e., 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 (Wilson, Szigeti et al. 2017) <sup>46</sup>. These psychotic disorders may be a separate diagnostic entity from PP that is stable over time and has distinctive psychopathological features.

In the present contribution, we aim to outline a novel and separate clinical entity, Substance-Related Exogenous Psychosis (SREP). As previously stated, the narrowed definition of SIP does not consider the issue of persistent psychoses that are clinically distinct from PP. Within this novel diagnostic category we refer to both transient and persistent forms of psychoses induced by substances (i.e., with onset following substance use). SREP can be considered a schizophrenia spectrum disorder but displays specific characteristics that clearly differentiate it from Schizophrenia/PP, in terms of clinical presentation, epidemiology, etiological models and treatment response.

**Substance Related Exogenous Psychosis: etiopathology and psychopathological models**

Epidemiological data regarding prevalence and distribution of SREP has highlighted relevant differences compared to primary psychoses. Prevalence rates of schizophrenia are similar around the world (American Psychiatric Association. 2013) <sup>38</sup>, whereas 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.

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 (Sass and Parnas 2003) <sup>47</sup>. 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 is a 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 the Karl Bonhoeffer’s hexogen model<sup>48</sup>. 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 open up a possible new scenario. When the thinking Ego has to face a recurring and intense abnormal experience (i.e., 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 south-eastern Asia. Methamphetamine-induced psychosis<sup>49</sup> is, in fact, a severe form of paranoid schizophrenia, in which the psychoma has become fully pervasive. (Wearne TA et al 2018)

### **Substance Related Exogenous Psychosis: clinical and psychopathological characteristics**

In terms of clinical presentation, SREP exhibits specific features. 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 PP in 400 participants with at least 1 psychotic symptom, use of alcohol and/or other drugs in the previous 30 days and no psychiatric inpatient history in the previous 6 months.<sup>50</sup> SIP patients 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. Other systematic studies aiming to characterize SIP as defined by DSM-5 and persistent, atypical psychotic disorders associated with substance use (i.e., SREP) are lacking and descriptions are mostly anecdotal. We briefly discuss possible distinctive clinical and psychopathological features associated with SREP, 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 or 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, affective symptoms. When normal consciousness is restored (i.e., the fields 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<sup>51</sup> (Vik, Cellucci, Jarchow & Hedt, 2004), and may help guide early differential diagnosis.

Modification of affectivity accompanied by depersonalization and derealization have been widely described<sup>52,53</sup> (G. Messas et al. 2018; Di Petta 2016). Several studies report affective symptoms (e.g., depressed mood, self-neglect and hostility) and suicidal ideation<sup>54,55,56</sup> (Akiyama, Saito, and Shimoda 2011; Fraser et al. 2012; Hides et al. 2015). Affective symptoms are possibly a core clinical feature of SREP and are not recognized in current diagnostic criteria<sup>57</sup> (Voce et al. 2019).

Delusions, mostly persecutory/paranoid, are usually secondary to abnormal perception resulting from a characteristic “sensorialization” of the world and of experience<sup>58,53</sup> (G. Messas 2013; Di Petta 2016). 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 post-modern determinants: a) hyperstability, a form of existence based on the experience of the present, cut off from the past and future; b) freezing of the sense of time, with inability to wait and invest in the future; c) hyper-materiality, where the sense of space and time are condensed in the present experience; d) non-evolving, crystallized delusions, that 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<sup>59,60, 53</sup> (Matsumoto et al. 2002; Martinotti et al. 2015; Di Petta 2016). 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, SREP patients appear more likely to interpret symptoms as a result of substance use compared to PP 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<sup>60</sup> (Martinotti et al., 2015b).

Aggressiveness appears to be transnosographic, probably representing an intrinsic element correlated with substance use. SREP patients generally have high levels of impulsivity and often display violent behavior and severe psychomotor agitation (e.g., bizarre/disorganized behavior and motor hyperactivity)<sup>50</sup> (Caton et al. 2005). 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 <sup>61</sup> (Goldstick, Stoddard, Carter, Zimmerman, et al 2016). 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 <sup>62</sup>(Johnson, Wu, Winder, et al 2016).

### **Substance Related Exogenous Psychosis: 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: dopamine (DA, mostly associated with psychedelic phenethylamines/synthetic cathinones); CB-1R activation (synthetic cannabimimetics); 5-HT<sub>2A</sub> receptor activation (tryptamine derivatives/hallucinogenic plants); antagonist activities at both NMDA and mGlu<sub>2/3</sub> 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 <sup>63, 64,65,66,67</sup>(Homman et al. 2018; Sullivan S, Herzig D et al., 2013; Kehr et al., 2011; Capriola, 2013; Lovrecic & Lovrecic, 2017). Users also reported positive effects (e.g., euphoria, improved psychomotor speed, alertness, and talkativeness) <sup>68,69,70</sup> (Deruiter WK, Cheng et al., 2013; Dargan PI, Albert S, et al, 2010; Mdege et al., 2017) . Cathinone-induced acute intoxication may include symptoms of the serotonin syndrome, such as aggression and hyperthermia, psychotic symptoms, catatonia and hyperactive delirium <sup>71,72,73,74,75,76,77,78</sup>(Warrick et al., 2013; Mugele et al., 2012; Hohmann et al., 2014; Denysenko et al., 2015; Otachbachi et al., 2010; Penders & Gestring, 2011; Weaver et al., 2015; Turner J, Mitchell JL et al., 2015; Penders et al., 2012). Mood disturbances and paranoid ideation have been observed in chronic users of cathinones. Rasmon Kalayasiri's study (2018)<sup>79</sup> reports that up to 40% of individuals who use methamphetamine may experience psychotic symptoms or paranoia.

Consistent with their pharmacological profile, those molecules that present with high serotonin: dopamine ratios may be considered analogous to entactogenic substances, such as MDMA. Conversely, high dopamine:serotonin ratios might predict a strong stimulant experience. Furthermore, high or low affinity to modulation of noradrenergic systems might

be associated with varying sympathetic nervous system activation, whereas activation of 5-HT<sub>2A/1A</sub> receptors would more likely predict hallucinogenic effects<sup>80</sup> (Baumeister et al., 2015).

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' (e.g., LSD) and psilocybin, 'psychotomimetics' (a term emphasizing 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 recognized by the patient not to be the result of external stimuli), together with intense emotional responses and thoughts that may influence the human psyche<sup>81</sup> (Schifano 2016). 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. A mood alteration towards hypomanic states may be reported, although suicidal thoughts and depression states may occur as well. The predominant clinical effects of tryptamines consist in 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. Less common are auditory, olfactory and gustatory hallucinations. Delusions with somatic themes are frequent: Ekbow, Capgras and Cotard syndromes have been reported, as well as episodes of demoniac possession and vexation. Psychotic negative symptoms are common. Mood is always flat, with affective blunting, anhedonia and a general sense of anesthesia and detachment from the surrounding environment is frequent. 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, 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 synthetic cannabinoids ("spice," "K2," and "kush"), generally CB<sub>1R</sub> and CB<sub>2R</sub> full agonists.

Whilst low-dosage levels of synthetic cannabinoids produce similar psychoactive effects to cannabis/THC, with higher dosages auditory/visual hallucinations, anxiety and intense feelings of paranoia often occur<sup>82,83</sup> (Bonaccorso et al, 2018; Winstock and Barratt, 2013a).

Other psychiatric and neurological effects include: behavioral dyscontrol and agitation<sup>84</sup>(Brakoulias, 2012); mood swings<sup>85</sup>(Celofiga et al., 2014); suicidal ideation, suicide attempts; panic attacks; thought disorganization; and hyperactive delirium<sup>86</sup>(Schifano et al., 2017). A florid/acute transient psychosis; relapse/worsening of a pre-existing psychosis and bipolar disorder<sup>87,88</sup>(Oluwabusi et al., 2012; Ustundag et al., 2015); and persistent psychotic disorder/‘Spiceophrenia’<sup>89,81</sup>(Papanti, Schifano, Botteon et al., 2013; Schifano et al., 2016) have all been described. Intoxication/acute toxic effects of SCs appear to be more akin to those experienced with sympathomimetic/stimulant drug use<sup>90,91</sup> (Wood and Dargan, 2012; Naviglio et al., 2015). It is interesting to note that some SCs exhibit pharmacologically relevant affinity for psychosis-associated receptors, including D2, 5-HT2A, or NMDA. Skryabin et al<sup>92</sup>(2019) 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; 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<sup>93</sup> (Suzuki and El-Haddad, 2017). Conversely, NSOs psychotropic effects include: anxiolysis; euphoria; feeling of relaxation; mood lift, dysphoric and dissociating effects<sup>94</sup> (Solimini et al., 2018) (Table 2). Other compounds classified among NSOs are desomorphine (‘krokodil’), mitragynine and 7-Hydroxymitragynine (alkaloids found in “kratom”/Mitragyna speciose)<sup>95</sup> (Megan A. Rech. Et al 2014) and salvinorin A, with its analogue herkinorin, which are the main *Salvia divinorum* components. Salvinorin A psychoactive effects include perceptual disturbances, psychosis, irritability and anxiety.

A range of experiences may be associated with gabapentinoid high-dosage abuse, including euphoria, improved sociability, opiate-like sedation, entactogenic feelings/dissociation and psychedelic effects<sup>81</sup> (Schifano et al., 2016).

These phenomena (serotonergic, dopaminergic and glutamatergic psychoma) cannot be considered as different syndromes, given the frequent overlap of symptoms among them. This is due to the fact that some NPS exert their effect on different pathways, and also because the possibility 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 (i.e., schizophrenia patients with SUD) and clinically distinct psychoses associated with substance use. Moreover,

psychotic phenomena following substance use in patients with a primary diagnosis of mood (bipolar) disorder or borderline personality disorder need to be recognized and clearly distinguished from other forms of psychoses. Also, early differential diagnosis and staging between persistent psychoses associated with substance use (i.e., 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, Substance-Related Exogenous Psychosis (SREP). SREP is conceived as a distinct psychotic disorder with its 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 (i.e., the contentious issue of long term antipsychotic medication in substance-related phenomena) (Dawson, et al 2008). 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 post-modern *liquid* society, marked by instantaneity and rapid transformation, where substance use is often an adaptive trait. Elements of post-modernity (i.e., 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.

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