Novel psychoactive substances and induced phenomena in psychopathology: the lysergic psychoma

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Summary

Novel psychoactive substances (NPS) are defined as new narcotic/psychotropic drugs that are not controlled by the United Nations’ Conventions on Narcotic Drugs (1961) or Psychotropic Substances (1971), but which may pose a comparable public health threat. The use of NPS is an emerging issue that will challenge psychopathology for years to come. The knowledge of health professionals about the acute/chronic physical and psychopathological manifestations associated with NPS intake is still scarce and fragmentary. The lysergic psychoma is a construct that may be pivotal in the understanding of phenomena induced by NPS in general, not only by lysergic hallucinogens. The model of hexogen psychosis developed by Karl Bonhoeffer may help to understand what happens during and after the intake of these substances. More clinical studies are needed to clarify these aspects and the importance of the hexogen model, not only in the perspective of toxic psychosis. This latter may represent a heuristic model that can help to better understand the psychotic process as a whole.

Key words

Novel Psychoactive Substances • Hallucinogens • Psychosis • Lysergic psychoma • Induced phenomena

Novel psychoactive substances: main groups and characteristics

Novel psychoactive substances (NPS) are defined as new narcotic/psychotropic drugs that are not controlled by the United Nations’ Conventions on Narcotic Drugs (1961) or Psychotropic Substances (1971), but which may pose a comparable public health threat. The adjective “novel” does not necessarily mean that these drugs have been synthesised in recent times; it mainly refers to substances that have lately gained popularity/availability in the recreational drugs market, becoming a reason of potential health concern. Many NPS are research chemicals, or even discarded products from pharmacological research that have been rediscovered and/or slightly modified to obtain effects similar to those of known illicit substances. In other words, NPS do not necessarily constitute new molecules/inventions. Moreover, NPS are often manufactured in unofficial laboratories and without any control on the hygienic standards of the productive process, raising further concerns for the presence of contaminating agents such as heavy metals or other licit/illicit drugs. Over the past 10 years, novel psychoactive substances have flooded the global market, and are advertised in head shops and over the Internet as ‘safer’ and ‘legal’ alternatives to illicit drugs. NPS are commercialised with marketing strategies specifically designed to attract customers, especially young people: colourful packaging, fun brand names, discounts and special offers are commonly used by NPS retailers. NPS misuse has been identified in 94 countries/territories; the number of European young people who declare to have ingested NPS at least once in their life has risen from 5% to 8% between 2011 and 2014. Compared to 2011, the countries where the consumption of new substances has increased the most are Spain (+8%), France (+7%) and Slovakia (+7%). So far, information on the short- and long-term effects of NPS is minimal or inaccurate, and what we are currently witnessing is that they can be just as harmful and addictive as illegal drugs such as cocaine, ecstasy and ketamine. Overall, NPS belong to a range of six categories (see Table I):

- synthetic cannabimimetics (‘spice’, ‘K2’ drugs);
- synthetic cathinones (‘meow meow’, ‘bath salts’ and others);
- latest generation phenethylamines/MDMA-like drugs, such as ‘fly’ drugs, NBOMe derivatives, DMAA and a range of indanes;

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### TABLE I.
NPS: typologies and psychopathological consequences.

<table>
<thead>
<tr>
<th>NPS category</th>
<th>Most popular compounds</th>
<th>Overall psychopathological consequences</th>
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</thead>
<tbody>
<tr>
<td>Synthetic cannabimimetics</td>
<td>“Spice”; “K2”; “Bonzai”; “Black mamba”; “Psyclone” etc.; including: AM-2201; AM-2233; AKB-48F; 5F-AB-PINACA; 5F-AKB-48; 5F-AMB; 5F-MN-18; 5F-PB22; 5F-SDB-005; 5F-SDB-006; AB-CHIMINACA; AB-FUBINACA; AB-PINACA; BB-22; EG-018; FAB-144; FDU-PB22; FUB-PB22; NM-2201; PB-22; THJ-018; THJ-2201 etc.</td>
<td>• Agitation/anxiety</td>
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<td>• Visual/auditory hallucinations</td>
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<td>• Altered mood and behaviour agitation; dysphoria; manic-like symptoms; and relapse of pre-existing bipolar disorders</td>
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<td>• Occurrence of florid/acute transient psychosis; relapse/worsening of a pre-existing psychosis; persisting psychotic disorders/'Spiceophrenia'</td>
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<td>• Suicidal ideation</td>
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<td>• Possible serotonin syndrome</td>
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<td>Synthetic cathinones</td>
<td>Mephedrone/meow; methedrone; methylone; 3-MeOMC; 3-MMC; 4-BMC; 4-MEC; 4-MeO-a-PVP; 4-MeO-PBP; 4-MeO-PV9; 4-MPD; 4F-PV8; 4F-PV9; 4F-PVP; a-PBT; a-PHP; a-PVT; dibutylone; DL-4662; ethylene; MDPPP; NEB; pentedrone; PV-8 etc.</td>
<td>• Increased alertness/euphoria hallucinations; agitation/aggression affective disturbances</td>
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<td>• Paranoid ideation possibly observed in chronic users</td>
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<td></td>
<td></td>
<td>• Decreased DA transporters on PET scans, suggesting the potential risk for long-term neuropsychiatric problems</td>
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<tr>
<td>Psychedelic phenethylamines (novel derivatives)</td>
<td>Fluoroamphetamine, PMA, 2C-T, 2C-B; ‘Bromodragonfly’; NBOMes; indanes; benzoturans (5; 6-APB/APDB; 5-EAPB; 5-MAPB; ‘BenzoFury’; etc.</td>
<td>• Euphoria/agitation</td>
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<td>• Psychosis/hallucinations</td>
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<td></td>
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<td>• Possible serotonin syndrome</td>
</tr>
<tr>
<td>Tryptamines (novel derivatives)</td>
<td>5-Meo-DALT (N,N-diallyl-5-methoxytryptamine); 5-MeO-DMT (5-methoxy,N,N-dimethyltryptamine), 5-MeO-DPT (5-methoxy,N,N-dipropyltryptamine); bufotenin; 5-Meo-aMT; 5-MeO-DMT; 5-IT</td>
<td>• Common visual hallucinations</td>
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<td>• Possible auditory hallucinations</td>
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<td></td>
<td>• Altered sensory perception/body image distortion/depersonalisation/marked mood lability/euphoria/relaxation/entactogenic properties/anxiety/panic disorder</td>
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<td></td>
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<td>• Possible serotonin syndrome</td>
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<td>Piperazines</td>
<td>BZP; mCPP; TFMPP</td>
<td>• Increased energy/irritability/anxiety/paranoid ideation</td>
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<td></td>
<td>• Hallucinations at high dosages</td>
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<tr>
<td>Others</td>
<td>Plants: e.g. Salvia divinorum; Kanna/Sceletium tortuosum; Mytragina speciosa/Kratom. Pharmaceuticals: e.g. gabapentinoids, phenazepam Performance and Image Enhancing Drugs (PIEDS): e.g., cognitive enhancers</td>
<td>• Salvia divinorum: euphoria/reduction of tension/libido enhancement/appetite suppression</td>
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<tr>
<td></td>
<td></td>
<td>• Kanna: empathogen; appetite suppressant; euphoria; hypertension; anxiety/irritability; perceptual/visual disturbances</td>
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<td></td>
<td>• Kratom: opiate-like sedation at higher dosages; possible perceptual/visual disturbances</td>
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<td></td>
<td>• Gabapentinoids’ high dosages: euphoria/improved sociability/sedation/opiate buzz/psychelic effects/entactogenic feelings/dissociation</td>
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<td>• Benzodiazepines: sedation; possible paradoxical effects (anxiety/irritability)</td>
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<td></td>
<td></td>
<td>• Cognitive enhancers: possible hallucinogenic/mood altering effects</td>
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• latest generation tryptamine derivatives such as 5-Meo-DALT, AMT;
• piperazines, e.g. BZP;
• other substances, such as herbs/plants (e.g., Salvia divinorum, Mytragyna speciosa/kratom); medicinal products, including a range of opiates/opioids, gabapentinoids, novel benzodiazepines/sedatives, stimulants and antiparkinsonians/anticholinergics; performance- and image-enhancing drugs, such as superstrength caffeine tablets, and cognitive enhancers.

Users are typically attracted by the intense psychoactive effects of these substances, and by the likely lack of detection in routine drug screenings. Indeed, these drugs act on a range of neurotransmitter pathways/receptors whose imbalance has been associated with psychopathological conditions, including dopamine, cannabinoid CB1, GABA-A/B, 5-HT2A, glutamate and k opioid receptors.

Synthetic cannabinoids (SCs) are a few hundred molecules designed to functionally resemble the effects of the main active compound of natural cannabis, Δ9-tetrahydrocannabinol (THC). SCs possess an extremely higher cannabinoid receptor binding affinity level than THC itself, with a significantly more intense dose-response efficacy. SCs mixtures are commonly sprayed over dried herbal material and smoked. According to data provided by the Substance Abuse and Mental Health Services Administration, in 2010 11,406 accesses to the emergency department in the US were due to synthetic cannabinoid consumption; the number of accesses has more than doubled in 2011 (28,531). Of these, 75% of emergencies involved young or very young patients, aged between 12 and 29 years old, predominantly males of emergencies involved young or very young patients, more than doubled in 2011 (28,531). Of these, 75% of emergencies involved young or very young patients, aged between 12 and 29 years old, predominantly males (79%) 6. The most commonly reported adverse effects are tachycardia, drowsiness/lethargy, agitation/irritability, vomiting, hallucinations/delusions, nausea, confusion, hypertension, chest pain and dizziness. Patients also reported disorganised behaviour, mood alterations, intense suicidal ideation and/or behaviour 7. SC intake has also been associated with the occurrence of florid/acute transient psychosis, relapse/worsening of a pre-existing psychosis and persisting psychotic disorders, the so-called “spiceophrenia”. 8.

Synthetic cathinones (SCath) are central nervous system stimulants, structurally similar to amphetamines/catecholamines and derived from the active compound cathinone, present in the plant Catha Edulis (known as Khat or Qat). The main cathinone derivatives are the semi-synthetic methcathinone and the synthetic compounds mephedrone, methylene and methylenedioxypyrovalerone (MDPV). Typically, SCath are snorted, ingested orally (“bombed”, namely swallowed after being wrapped in cigarette paper) or injected. The main effects of synthetic cathinones on CNS are mainly due to their ability to act on monoamine reuptake, determining an increase of dopamine, serotonin and noradrenaline at a synaptic level 9. More than half of mephedrone users experience both physical and psychological unwanted effects, including nausea, vomiting, flushing, sweating, tremors, headache, blurred vision, restlessness and anxiety 10. Other referred serious adverse effects of mephedrone include hyperthermia, rhabdomyolysis, renal failure, seizures and arrhythmias. Chronic users also report mood disturbances and paranoid ideation 11. Synthetic cathinones appear to be peculiarly involved, more than other NPS, in the development of both self- and other-oriented violent behaviours: a number of case reports in human users of cathinone drugs highlighted that they tend to produce increased aggression, including suicide 12.

Other NPS include piperazines, whose effects are similar to those of amphetamine but slightly less intense; psychedelic phenethylamines/MDMA-like drugs (2C drugs; Fly drugs), which enhance mood, increase energy and talkativeness and cause perceptual alterations; tryptamines, whose main effects are due to their agonist activities on 5-HT2A receptors and serotonin transporter inhibition, and consist in visual hallucinations, altered perceptions, body image distortion, derealisation/depersonalisation, marked mood lability; natural (Ayahuasca, Salvia divinorum) and pharmaceutical products (e.g. gabapentinoids, phenzepam), which encompass a wide range of substance-specific desired and untoward effects.

NPS intake and psychopathological issues

The recent development of a huge number of NPS, combined with the ability of the Internet to spread information quickly, represents a global and unprecedented challenge for both public and mental health. The knowledge of health professionals on the acute/chronic physical and psychopathological manifestations associated with NPS intake is still scarce and fragmentary. Moreover, a further alarming trend may derive from misuse of novel psychoactive substances in young psychiatric patients: NPS may reduce the adherence to therapeutic plans and the efficacy of treatments for psychiatric disorders, and may also worsen the symptoms of a pre-existing pathology 13.

NPS may precipitate the imbalance of a wide range of neurotransmitters/pathways/receptors; e.g. dopamine/DA (mostly associated with the intake of 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 receptors’ activation (Salvia divinorum) (Table I). With regards to the most frequently observed clinical features related to NPS consumption,
anxiety, dysphoria, increased aggression, mood fluctuations and perceptual/thought disturbances are to be mentioned. As previously stated, a number of recent studies have highlighted a close relation between synthetic cannabimimetic use and the onset of schizophrenic-like symptoms. Scientific research has recently focused on induced psychotic experiences in the past few years. The study by Caton et al. aimed at identifying key demographic, family and clinical differences in substance-induced psychosis and primary psychotic disorders 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 before the previous 6 months. Of this sample, 44% was diagnosed with a substance-induced psychosis, while 56% with a primary psychosis. The patients included in the substance-induced psychosis group had more common visual hallucinations, a higher prevalence of suicidal thoughts during the previous year, more common violent behaviour, more frequent family history of substance abuse and higher levels of insight.

Other studies have described psychotic states induced by methamphetamine consumption (methamphetamine-associated psychosis, MAP), characterised by paranoid delusions and visual/auditory hallucinations, with an enhanced vulnerability to relapse of psychosis and very long duration of vulnerability to relapse. Paranoia appears to occur increasingly rapidly in the course of a session of methamphetamine use. Moreover, the severity of methamphetamine dependence and antisocial personality disorder appear to be predictive of methamphetamine-induced psychosis.

The number of subjects not recovering from the induced episodes is relevant, opening the question about the relationship between substance abuse, particularly if continuous and at high dosages, and development of a full psychosis. With regards to this, the model of hexogen psychosis and its toxic subtype, frequently reported as lysergic psychoma, may be helpful to shed light on the issue.

**The lysergic psychoma**

The lysergic psychoma is a construct that may be pivotal in the understanding of phenomena induced by NPS in general, not only by lysergic hallucinogens. This term, which was used for the first time by Cargnello and Callieri in 1963, has its roots in the definition made by Hellpach and, most of all, in the Karl Bonhoeffer’s hexogen model. The term “lysergic psychoma” describes a syndrome characterised by a clear egodystonic experience in which the subject perceives the presence of a “foreign body” in his own 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 of its role, and usually tries to stem and contain the overflowing psychoma.

This experience is usually self-limiting, in line with what is considered an induced phenomenon, and considering the transient pharmacodynamic effects exerted by the substance. However, taking into account its repetitive nature, the high dosages and long-lasting pharmacokinetic properties of novel compounds, a new scenario may be hypothesised. If the thinking Ego has to face a stable and repetitive abnormal experience, its resilience and its capacity to contain it might be overcome. If unusual thoughts or deviant perceptions become permanent, the capacity to deflate them is reduced to be more and more inadequate. The thinking Ego may not able to counteract the psychoma anymore, and the latter can invade the functioning part of one’s mind, becoming fully pervasive. This could be the beginning of a psychotic experience, an epidemic diffusion inside the brain.

**Karl Bonhoeffer and the hexogen model of psychosis**

Karl Bonhoeffer included the lysergic psychoma among the models of hexogen psychosis in which an external noxa may determine and directly influence the development of a full psychosis. Bonhoeffer firstly described this phenomenon while working in Breslau with alcoholic patients, under the supervision of Wernicke. His aim was to identify the base of a functional dysfunction, a hexogen complex that could interact with an endogenous background and then produce a full psychosis. Bonhoeffer subsequently moved to the University of Berlin, where he fully developed the concept of a hexogen reaction, rather uniform, determined by an external noxa, which could be toxic, infective, traumatic or degenerative. The core characteristic he considered was impaired consciousness, ranging from confusion and dreamlike experiences to delirium and stupor. Bonhoeffer’s hexogen model was generated in a dialectic relationship with Bleuler’s endogenous model, in the same period of Bleuler’s first use of the term schizophrenia. Schizophrenia has in itself the idea of prozess, including the aspects of progression, worsening and cognitive decline deeply influenced by Kraeplin. The concept of prozess was subsequently related to the emergence of the proposals of sterilisation and euthanasia for psychiatric patients. The hexogen model was not necessarily to be considered negative and progressive, and this is one of the reasons for its misfortune. In 1938, Bonhoeffer did not adhere to the euthanasic approach for psychotic patients promoted
by the Nazi Party. His hexogen model did not fit with the concept of a progressive pathway towards deterioration and social uselessness: his school was therefore dismissed after 1938 when he left the University of Berlin in favour of Max de Crinis.

The exogenous model of psychosis was never developed in greater detail, while the endogenous one influenced all German psychopathology and still constitutes the basis of the main diagnostic approaches. The lack of attention paid to the school of Bonhoeffer, which was not consistent with the myth of chronicity and its fatal progression, was anyhow extremely negligent, and his reflections deserve a better understanding, not only from the perspective of toxic experiences. The exogenous model moved from Germany and found more interest in France, UK, Scandinavia and Italy. The endogenous model and the Kraepelinian approach remained, however, the official model in Germany, and obtained the role of the main theoretical approach for psychosis until now.

**Morselli and the lysergic psychotic experience**

In Heidelberg, in 1927, Kurt Beringer, a pupil of Bonhoeffer, developed the idea of psychoma in relation to mescaline and other lysergic drugs. In Italy, Giovanni Enrico Morselli in 1932 ingested mescaline and reported its effects in a number of essays, in which the hexogen model of psychoma was fully explained in relation to a toxic phenomenon. Morselli also described the clinical effects induced by LSD on a sample of volunteers, including himself. He reported a long-lasting syndrome, characterised by visual hallucinations, delusional perceptions and paranoid thinking. This experience was compared to schizophrenia, with the altered perceptive experience as the main link.

**The lysergic psychoma: typologies and characteristics**

The lysergic psychoma is an exogenous clinical expression that almost all NPS users may undergo, regardless of the specific chemical class of the substance. Of course, the pharmacodynamics of the drug taken is responsible for the specificity of the possible abnormal induced phenomena.

Substances acting predominantly on serotonergic pathways are most commonly implicated in the development of visual hallucinations with vivid colours, frequently associated with intense emotional experiences, either positive or negative. 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.

Substances mainly acting on dopaminergic pathways are primarily associated with paranoid thought 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. Substances mainly acting on glutamatergic pathways usually determine dissociative reactions, such as derealisation and somatopsychic depersonalisation. Visual abnormal perception may be reported, mainly in the form of distortions and illusions. Bodily and kinesthetic hallucinations are frequent, as 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 anaesthesia and detachment from surrounding environment is frequent. Irritability and aggressiveness may be noted.

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 potential on different pathways, and also because the possibility of polyabuse is the norm rather than the exception. However, the ability to differentiate and characterise clinical presentation may be useful to plan an appropriate therapeutic approach.

With regards to clinical management, the dopaminergic psychoma is the one most frequently reported as long-lasting and with the worse prognosis, as described for shaboo and methamphetamine users in south-eastern Asia. Methamphetamine-induced psychosis is, in fact, a severe form of paranoid schizophrenia, in which the psychoma has overflowed well beyond its limits.

**Conclusions**

The use of NPS is an emerging issue that will challenge psychopathology for years to come. The onset of psychiatric symptoms after the use of these potent and highly rewarding drugs appears to be the norm, especially in the long term. These episodes, sometimes with clear psychotic features, are often reversible; however, when the use is frequent, persistent, and at high dosages, the onset of full and long-lasting disorders is commonly observed. The model of hexogen psychosis developed by...
Karl Bonhoeffer may help to understand what happens during and after the intake of these substances. A foreign body perceived in the mind of the subject, the so-called lysergic psychoma, may be an experience in which the thinking Ego is still able to match and contain the abnormal part. However, when the psychoma is enduring, the Ego resilience may be overcome, opening the doors to a full psychotic experience. More clinical studies are needed to clarify these aspects and the importance of the hexogen model, not only in the perspective of toxic psychosis. This latter may represent a heuristic model that can help to better understand the psychotic prozess as a whole.

References