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PRACTICE



CLINICAL UPDATES

Novel psychoactive substances: types, mechanisms of action, and effects

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In 2016 the Psychoactive Substances Bill banned trading but not possession of all current and future novel psychoactive substances (NPS), sometimes incorrectly called “legal highs,” in an attempt to overcome rapid proliferation of these compounds. Over 560 substances are currently monitored by the European Monitoring Centre for Drugs and Drug Addiction, with 100 new agents identified in 2015 alone. Stimulants and synthetic cannabinoids account for the vast majority and are the types most commonly clinically encountered.¹ Online purchases are increasing according to the 2016 Global Drug Survey,² potentially in response to legislative changes, as is overall NPS use: lifetime consumption was reported by 8% of younger individuals in 2015, up from 5% in 2011, with figures relatively similar between sexes and different countries.³

Professionals report feeling less confident about managing NPS compared with established recreational drugs.⁴ There were 15 485 accesses to UK National Poisons Information Service TOXBASE relating to “legal highs,” “branded products,” synthetic cannabinoids, and mephedrone in 2014–15.⁵ Regarding harms from longer term dependence, the UK National Drug Treatment Monitoring System (NDTMS) report in 2015 described 3048 and 1370 adults with documented problematic use of mephedrone and “other” NPS respectively.⁶

Information on NPS primarily stems from case reports and case series. However, there is evidence that risks associated with NPS are often different from those seen with established recreational drugs. This article classifies NPS into their major groupings and provides information on the desired effects of these compounds, their pharmacology, and the risks associated with their use. The linked Practice article⁷ provides advice on what to ask and do when consulting with a patient who may be using NPS.

What are NPS and how do they work?

NPS are compounds designed to mimic existing established recreational drugs such as “ecstasy” (MDMA) and cannabis. Before changes in the law, manufacturers would tweak the pharmacological structure of existing compounds to create a new “legal” substance, which earned them their familiar name “legal highs.” There is no universally agreed way to categorise NPS. However, they can be broken down into four, somewhat overlapping, main categories: stimulants, cannabinoids, hallucinogens, and depressants.

Stimulant NPS (fig 1)

Stimulants are taken to produce a sense of euphoria and wellbeing, or “a high.” This is one of the largest NPS groups, typically sold as powders or pills. Mephedrone is the most commonly available variant. They are structurally related to MDMA (ecstasy), cocaine, and amphetamines and can be swallowed (users often talk about “bombing,” when the drugs are swallowed wrapped in paper), inhaled (“snorting”), and, less commonly, injected or administered rectally.

Stimulants increase synaptic levels of serotonin, dopamine, and/or noradrenaline. Agents act as neuronal reuptake pump inhibitors or as active releasers, and each has a unique effect on neurotransmitter concentrations.^{8 9} Neurotransmitter releasers are associated with greater addiction and neurotoxicity.^{10 11} NPS variants, such as the large cathinone family, are commonly associated with enhanced neurotoxicity compared with traditional stimulants.^{9 12}

The ratio of serotonin to dopamine activation is important in achieving the desired effects. The more serotonergic drugs, similar to ecstasy, produce more empathy and emotional

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Infographic: Visual summary of the main categories of novel psychoactive substances

What you need to know

- Novel psychoactive substances (NPS, “legal highs”) are compounds designed to mimic existing established recreational drugs. They can be grouped into four main categories: stimulants, cannabinoids, hallucinogens, and depressants
- Legislation regarding NPS varies internationally. In the UK it is now illegal to distribute or sell NPS, but possession is not a criminal offence
- NPS should not be regarded as safer than established recreational drugs
- The most commonly clinically encountered NPS are stimulants (such as mephedrone) and cannabinoids (such as “spice”)
- Psychiatric and rehabilitation units, prisons, and schools face particular challenges in detecting and preventing use

Sources and selection criteria

- We searched Medline and Embase for publications using the terms “legal highs,” “NPS,” and “novel psychoactive substances”
- The subject is challenging to appraise: there is a dearth of information on the hundreds of new compounds, much being case based reports; drug effects are inherently subjective, and it can be complex to engage drug consumers in an area concerning quasi-illegal behaviour. Where possible, systematic reviews were consulted.
- Much of the information on the topic is in non-scientific publications such as governmental and other agencies’ reports, including from the European Monitoring Centre for Drugs and Drug Addiction, “grey” non-peer reviewed sources such as the Global Drug Survey, and on user discussion forums such as Erowid.

openness.^{13 14} More dopaminergic drugs, similar to cocaine, produce more euphoric and mania-like experiences.¹⁵ Some NPS stimulants, such as the NBOMe- and 2C-series, also produce psychedelic or hallucinogenic experiences.^{16 17}

Risks

Acute adverse presentations are most commonly associated with agitation, anxiety, psychotic symptoms, hypervigilance, cardiovascular toxicity (arrhythmias and hypertension), and hyperthermia. Case reports also describe seizures, delirium, and renal and respiratory failure following ingestion.¹⁸⁻²¹ Serotonin syndrome—autonomic instability, confusion, and neuromuscular problems—can be life threatening and is particularly associated with use of multiple serotonergic recreational drugs, or concomitant use of serotonergic prescription medication or over the counter medicines such as St John’s wort.^{15 22}

Long term, traditional stimulants are associated with impulsive behaviour, abuse, and dependency,¹⁵ and NPS stimulants seem no different.²³ Depression and cognitive impairments are recognised sequelae,²⁴ and there are case reports of psychoses.^{25 26} Cessation can lead to a psychological withdrawal syndrome of fatigue, insomnia, lethargy, flu-like symptoms, impaired concentration, and lability of mood.²³ There is considerable variation between individuals, but such outcomes are more commonly associated with longer term and more regular drug use.

Cannabinoid NPS (fig 2)

Cannabis is the most widely used established recreational drug.¹ NPS variants are the synthetic cannabinoid receptor agonists (SCRAs), and there are over 150 different SCRAs available, usually sold having been sprayed onto herbal mixtures that are smoked. They are sometimes referred to as “spice” or “noids.” Liquid SCRAs also exist for use in electronic cigarettes and vapourisers. They produce a pleasant state of relaxation and of feeling “stoned.”

The major psychoactive component of cannabis is tetrahydrocannabinol, a partial agonist at cannabinoid receptors that ordinarily have roles in neuronal homeostasis and immune functioning.²⁷ However, SCRAs are typically full agonists of, and bind in a different pattern to, cannabinoid receptor subtypes. SCRAs also lack cannabidiol, an antipsychotic and anxiolytic compound found in cannabis that dampens some of the effects of tetrahydrocannabinol. These pharmacological differences

may explain the variation in the subjective and physiological effects of SCRAs compared with cannabis.²⁸⁻³⁰

Risks

As well as a subjective effect of feeling stoned, cannabis and SCRAs can be both stimulating and sedating, anxiogenic and anxiolytic.^{27 31} Both can cause anxiety, paranoia, and psychotic symptoms.^{32 33}

Side effects have been reported more frequently with SCRAs than with cannabis,²⁸ and, as they are most commonly sprayed onto compounds for smoking, their strength and effects can be less predictable. Some highly potent agents can induce considerably agitated states.³¹ Unlike cannabis, some produce a “hangover” state.³⁴ Emergency department case reports describe additional features with SCRA use not typically seen with cannabis, such as confusion and cognitive impairment, slurred speech, and excessive sweating, as well as symptoms of stimulant toxicity (hypertension, tachycardia),^{32 35} renal failure, pulmonary damage, myocardial infarction, seizures, and stroke.³²⁻³⁸

In the longer term, cannabis is not traditionally considered to produce physical dependency, though individuals can demonstrate a psychological dependency.³⁹ Case reports and user discussion forums suggest that SCRAs have a higher potential for addiction and withdrawal effects.⁴⁰⁻⁴²

Hallucinogenic NPS (fig 3)

Hallucinogens fall into two subcategories—dissociatives and psychedelics (or classical hallucinogens). Dissociatives are particularly associated with harmful side effects.

Dissociatives

Dissociatives produce a unique euphoric “dissociated” state, with a perception of an absence of time, weightlessness, and disconnection from the physical body. They can be inhaled, swallowed, or injected. The first agents in this class, ketamine and phencyclidine (PCP), were originally used as general anaesthetics, but they have generally been discontinued because of postoperative dissociative side effects. The spectrum of NPS dissociatives runs between some milder than ketamine to others as strong as phencyclidine.¹⁰ The common variant methoxetamine (sometimes called “mexxy”) is generally reported to produce more intense and longer lasting dissociative effects than ketamine.⁴³ In extremis, users may enter an “m hole”

(similar to a “k hole” with ketamine), a state of profound dissociation that some people find highly pleasurable and others unpleasant.¹⁰⁻⁴⁷ They primarily act as uncompetitive antagonists at glutamatergic NMDA receptors,⁴⁸ but also bind at opioid and monoaminergic receptors.¹⁰

Risks

Most risk data come from the parent compounds ketamine and phencyclidine, though the evidence emerging from NPS case studies literature fits with these.⁴⁶⁻⁴⁷ Deaths are primarily accidental, through impulsive and careless behaviours,¹⁰ although there are reports of fatalities directly linked to methoxetamine toxicity.⁴⁹⁻⁵⁰ Consistent with ketamine and phencyclidine, there are case reports of aggressive, psychotic, and catatonic states with dissociative NPS use, acute cerebellar toxicity, cardiovascular incidents, and renal and acute respiratory failure.¹⁰⁻⁵¹ Methoxetamine was anecdotally sold as a physically safer alternative to ketamine, but there is limited evidence to support this currently.⁵⁰

Longer term, dissociatives often produce considerable cravings and binge consumption patterns, although there is some evidence that methoxetamine may be less addictive than ketamine.⁵⁰ Long term sequelae of use can include neurocognitive deficits and deterioration in mood.⁵²⁻⁵³ Physical health complications include abdominal pain (“M cramps”), nausea, vomiting, and diarrhoea; cardiovascular problems of arrhythmias and blackouts¹⁰; and severe ulcerative cystitis and renal damage.⁵⁴

Psychedelics

These agents typically do not produce true hallucinations, but are associated with a range of “psychedelic” effects, including perceptual alterations and quasi-mystical experiences sometimes categorised under the headings of “oceanic boundlessness” and “anxious ego dissolution.”⁵⁵⁻⁵⁶

These exert their effects primarily as an agonist at the 5-HT_{2A} receptor. There is some evidence they may also act on 5-HT_{1A} and heteromer receptor complexes.⁵⁶ Traditional agents include LSD and psilocybin; most NPS psychedelics, such as 5-MeO-DALT and the NBOMe- or 2C-series, also have stimulant effects.¹⁰⁻⁵⁸

Risks

Psychedelics generally have a low risk-profile compared with both other established recreational drugs and NPS. Consumers seldom present acutely to clinical services, though acute intoxication may contribute to adverse mood reactions.⁵⁶ Unlike established recreational psychedelics, some NPS hallucinogens also have stimulant properties, and these have increased risk of acute toxicity, including agitation, hallucinations, tachycardia, hypertension, hyperthermia, rhabdomyolysis, serotonin syndrome, and seizures.⁵⁷⁻⁶¹ There is currently little evidence of longer term health risks or addiction.⁵⁶

Depressant NPS (fig 4)

Depressant NPS subcategories—benzodiazepines and opioids—seem to carry a similar picture for acute emergency presentations but differ in their mental health implications. They are generally sold and consumed in pill or powder form. They are perhaps the least understood of the NPS. This may be because they are so similar to established recreational drugs that clinicians may not be aware that an individual has used an NPS version. NPS benzodiazepines include diclazepam and flubromazepam. Fewer NPS opioids have appeared in isolation,

but they may be sold as part of NPS cannabinoid smoking mixtures, as has been reported for AH-7921.⁶²

Benzodiazepines

These are positive allosteric modulators of the GABA receptor, enhancing inhibitory signalling in the central nervous system.¹⁰ Alcohol has a similar pharmacodynamic mechanism and can potentiate their effects.¹⁰ Acutely, NPS benzodiazepines have similar clinical effects to established compounds such as diazepam, with sedative, anxiolytic, hypnotic, and anticonvulsant properties. Some users of NPS benzodiazepines report that they have much longer durations of actions and effects than established agents, and several compounds have long half lives (flubromazepam, for example, having a half life of 100 hours⁶³). While this reduces dependency potential, unwanted effects can persist for a long time and there are greater risks of accidental overdose. There are reports of NPS benzodiazepine induced confusional states lasting several days.⁶⁴ Acute withdrawal may cause seizures.⁶⁵ Long term use is associated with risk of addiction and impaired cognition,⁶⁶ physiological and mental health sequelae consistent with traditional benzodiazepines.⁶⁵

Opioid NPS

Little is known about any specific subjective effects of NPS opioids to differentiate them from established recreational opioids. However, self experimentation reports suggest that some can have much longer durations of action.⁶⁷⁻⁶⁸ They exert their euphoric effects through presynaptic μ -opioid receptors. Novel agents such as AH-7921, MT-45, and novel fentanyl seem to have similar mechanisms of action.⁶⁷⁻⁶⁹

Case reports of NPS overdoses are congruent with those of traditional opioids, though animal data suggest AH-7921 has a higher overdose risk than morphine.⁶⁷ Both human case series and animal studies have shown that naloxone can reverse the toxicity seen with novel opioids, although the doses of naloxone required may be higher than for traditional opioids, particularly in cases of novel fentanyl toxicity.⁶⁷⁻⁷¹ There have been reports of unusual toxicity related to the use of MT-45, including short-to-medium term hearing loss.⁷¹

No long term NPS risk data exist, though animal models have shown AH-7921 to be similar to morphine in addictive potential and withdrawal effects,⁶⁷ and MT-45 and novel fentanyl are probably similar.

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Contributors: All authors have made substantial contributions to the conception and design of the work; drafted and revised the work critically for important intellectual content; approved the final version to be submitted; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. DKT is the guarantor of the article.

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Priorities for future research

- More robust data on epidemiology and links to acute and long term harms
- Evaluating the demands and effectiveness of existing drug treatment services to manage harmful or problematic NPS use
- Long term development of pharmacological treatments for dependency: currently only available for opioids and benzodiazepines, though there is work on cannabinoid and stimulant agents
- Determining any adverse neurodevelopmental impact on younger users

Information for patients who ask about NPS

- In the UK the Psychoactive Substances Bill states that individuals will be prosecuted for trading, but not possession, of NPS. It is uncertain how monitoring and enforcing will work in practice, but one effect is that supply chains will move away from high street "head shops"
- NPS do not seem to be safer or less harmful than established recreational drugs, either in the short or longer term, though there is considerable variation in risks between individual NPS and classes of NPS
- If using a novel substance, as with any drug, start with a very small dose and increase if necessary to obtain desired effects
- Individuals can have very different responses to the same drug, and combining with other recreational, prescription, or over the counter drugs or alcohol can increase risks
- Seek urgent medical help if you or a friend feel unwell after using a NPS (as with any recreational drug). Call 999 for an ambulance; take the compound or any information on it with you if possible

Resources for healthcare professionals

- UK National Poisons Information Service (www.npis.org) and its clinical toxicology database TOXBASE (www.toxbase.org)—If you need advice or information that is not available on TOXBASE then call NPIS for clinical support
- NEPTUNE (novel psychoactive treatment: UK network) (<http://neptune-clinical-guidance.co.uk>)—Comprehensive clinical guidance on party drugs
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- GOV.UK. New Psychoactive Substances (NPS) resource pack (www.gov.uk/government/publications/new-psychoactive-substances-nps-resource-pack)—UK Home Office NPS resource pack for "informal educators and frontline practitioners"
- EMCDDA. EU drug markets report (www.emcdda.europa.eu/start/2016/drug-markets)—Guide to the European illicit drugs' market

Resources for drug consumers and the public

- FRANK (friendly confidential drugs advice). Legal highs (www.talktofrank.com/legalhighs)—UK based general information guide for patients and the lay public
- EROWID (www.erowid.org)—Non-profit, international, drug-consumer-led website providing non-judgmental advice and guidance
- Rise Above (<http://riseabove.org.uk/tag/drinking-smoking-drugs/>)—Website by NHS England for children and adolescents about substance misuse, mental health, and other social issues
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- Global Drug Survey (www.globaldrugsurvey.com)—Information for, and international survey of, NPS consumers
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How patients were involved in the production of this article

A patient with long term harmful use of NPS, including significant associated mental ill health, was involved in the initial design of this article. This particularly helped frame the discussion on the potential harms of these compounds. The patient wishes to remain anonymous.

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Figures

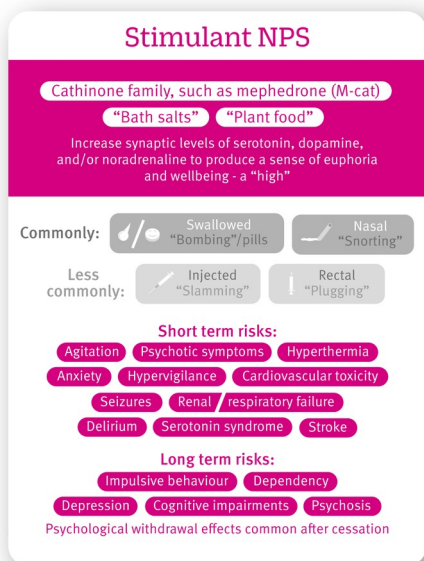


Fig 1 Visual summary of stimulant NPS

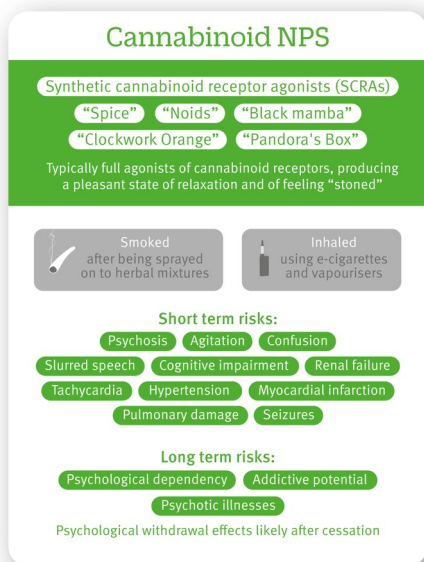


Fig 2 Visual summary of cannabinoid NPS

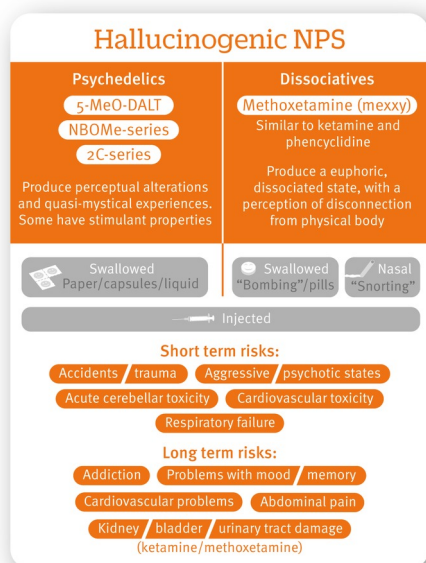


Fig 3 Visual summary of hallucinogenic NPS

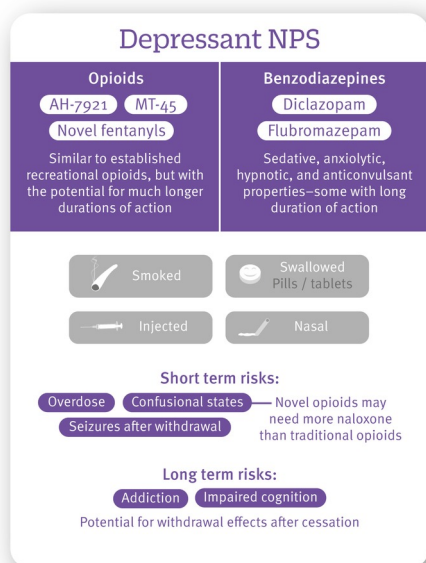


Fig 4 Visual summary of depressant NPS