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 noradrenaline. Agents act as neuronal reuptake pump inhibitors or as active releasers, and each has an unique effect on neurotransmitter concentrations.7,8 Neurotransmitter releasers are associated with greater addiction and neurotoxicity.9,10 NPS variants, such as the large cathinone family, are commonly associated with enhanced neurotoxicity compared with traditional stimulants.11,12 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...
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. More dopaminergic drugs, similar to cocaine, produce more euphoric and mania-like experiences. Some NPS stimulants, such as the NBOMe- and 2C-series, also produce psychedelic or hallucinogenic experiences.

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. 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.

Long term, traditional stimulants are associated with impulsive behaviour, abuse, and dependency, and NPS stimulants seem no different. Depression and cognitive impairments are recognised sequela, and there are case reports of psychoses. Cessation can lead to a psychological withdrawal syndrome of fatigue, insomnia, lethargy, flu-like symptoms, impaired concentration, and lability of mood. 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. NPS variants are the synthetic cannabinoid receptor agonists (SCRAs), and there are over 150 different SCRA s available, usually sold having been sprayed onto herbal mixtures that are smoked. They are sometimes referred to as “spice” or “noids.” Liquid SCRA s 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. However, SCRA s are typically full agonists of, and bind in a different pattern to, cannabinoid receptor subtypes.

SCRA s 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 SCRA s compared with cannabis.

Risks

As well as a subjective effect of feeling stoned, cannabis and SCRA s can be both stimulating and sedating, anxiogenic and anxiolytic. Both can cause anxiety, paranoia, and psychotic symptoms.

Side effects have been reported more frequently with SCRA s than with cannabis, 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. Unlike cannabis, some produce a “hangover” state. Emergency department case reports describe additional features with SCRA use not typically seen with cannabis, such as confusion and cognitive impairment, slurred speech, and, except for SCRA s may explain the variation in the subjective and physiological effects of SCRA s compared with cannabis.

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. The common variant methoxetamine (sometimes called “mexxy”) is generally reported to produce more intense and longer lasting dissociative effects than ketamine. In extremis, users may enter an “in hole”
Flubromazepam. Fewer NPS opioids have appeared in isolation,
version. NPS benzodiazepines include diclazepam and
clinicians may not be aware that an individual has used an NPS
are generally sold and consumed in pill or powder form. They
opioids—seem to carry a similar picture for acute emergency
depression and addition.

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

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

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.” These exert their effects primarily as an agonist at the 5-HT2A receptor. There is some evidence they may also act on 5-HT1A
heteromer receptor complexes. Traditional include LSD and psilocybin; most NPS psychedelics, such as
5-MeO-DALT and the NBOMe- or 2C-series, also have
stimulant effects.

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. 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. There is currently little evidence of
longer term health risks or addiction.

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 diazezapem and
flubromazezapem. 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.

Benzodiazepines
These are positive allosteric modulators of the GABA receptor,
enhancing inhibitory signalling in the central nervous system. Alcohol has a similar pharmacodynamic mechanism and can
potentiate their effects. 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
(flubromazezapem, for example, having a half life of 100 hours). 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. Acute withdrawal may
cause seizures. Long term use is associated with risk of
disability, and impaired cognition, physiological and mental
health sequelae consistent with traditional benzodiazepines.

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. They exert
euphoric effects through presynaptic μ-opioid receptors. Novel
agents such as AH-7921, MT-45, and novel fentanyls
seem to have similar mechanisms of action. 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. 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. There have been reports of unusual toxicity related to the use of MT-45, including
short-to-medium term hearing loss.

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, and MT-45 and novel fentanyls are
probably similar.

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1 European Centre for Disease Prevention and Control. Annual report.

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
- NEPUNE (novel psychoactive treatment: UK network) (http://neptune-clinical-guidance.co.uk)—Comprehensive clinical guidance on party drugs

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/drinkingsmokingdrugs)—Website by NHS England for children and adolescents about substance misuse, mental health, and other social issues
- Bowden-Jones O. The Drug Conversation: How to talk to your child about drugs. Royal College of Psychiatrists, 2016
- Global Drug Survey (www.globaldrugsurvey.com)—Information for, and international survey of, NPS consumers

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

**Stimulant NPS**

- Cathinone family, such as methylphenidate (i.e. “Eutylone”)
- “Plant food”
- Increase synaptic levels of dopamine, serotonin, and/or noradrenaline to produce a sense of euphoria and wellbeing - a "high"

**Commonly:**
- Swallowed “tobacco / pills”
- Nosal “snorting”

**Less commonly:**
- Injected “snorting”
- Rectal “plastic”

**Short term risks:**
- Tachycardia
- Hypertension
- Hypothermia
- Anxieties
- Vomiting
- Cardiovascular instability
- Seizures
- Renal / respiratory failure
- Confusion
- Seroquel syndrome
- Strokes

**Long term risks:**
- Insomia / depression
- Dependent
- Coma
- Other medical conditions
- Psychosis

Psychological withdrawal effects common after cessation

**Cannabinoid NPS**

- Synthetic cannabinoid receptor agonists (SCRAIs)
  - "Spice"
  - "Noids"
  - "Black mamba"
  - "Clockwork Orange"
  - "Pandora’s Box"

Typically full agonists of cannabinoid receptors, producing a pleasant state of relaxation and feeling *“stoned”*

- Smoked after being sprayed on to herbal mixtures
- Mixed with incense / cigarettes and other substances

**Short term risks:**
- Psychosis
- Agitation
- Confusion
- Superspeed
- Cognitive impairment
- Renal failure
- Impaired
- Depression
- Gastrointestinal dysfunction
- Gastrointestinal bleeding
- Seizures

**Long term risks:**
- Psychological dependence
- Addictive potential
- Psychotic diseases

Psychological withdrawal effects likely after cessation

**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