

Novel psychoactive substances

There has been a major increase in the number of new drugs of abuse on the global illicit drugs market, including in Norway. These substances are referred to as «novel psychoactive substances» (NPS), and are mainly sold over the Internet. Potent substances in uncertain doses entail a risk of inadvertent overdoses and thus serious poisonings and deaths. In this article we provide a knowledge status for these substances.

What are referred to as «novel psychoactive substances» (NPS) are chemical substitutes for traditional drugs of abuse (Figure 1) (1). To some extent, these new agents include very potent substances that may cause serious mental reactions and lethal poisonings. Because of a dearth of knowledge of their effects and of how poisonings manifest themselves and should be treated, these intoxicants constitute a major challenge to the health services. The phenomenon of novel psychoactive substances and the challenges associated with them are also described in a «Perspectives» article in this issue of the Journal of the Norwegian Medical Association (2).

This article is based on a discretionary selection of articles found through a literature search in PubMed. In addition, we have included reports from Norwegian and European authorities.

Categorisation of novel psychoactive substances

These drugs constitute an extremely heterogeneous group of substances, which in terms of their pharmacological and chemical properties can be categorised in many different ways. We will base our review on the categorisation used by the European Centre for Drugs and Drug Addictions (EMCDDA), with an emphasis on the following main groups: phenethylamines, cathinones, piperazines, tryptamines, synthetic cannabinoids and «other substances» (Figure 2).

In our categorisation, benzodiazepines, opioids and arylamines fall within the group of «other substances». GHB (gamma-hydroxybutyrate) is no longer considered a novel psychoactive substance and is therefore not included in this review.

Phenethylamines

Phenethylamines encompass a large number of substances with a molecular structure and effects similar to those of amphetamine. They are sold under separate names or as ecstasy and amphetamine (3). This group also includes amphetamine, methamphetamine, parame-

thoxymethamphetamine (PMMA) and methylenedioxymethamphetamine (MDMA), which is also known as the active ingredient in ecstasy.

Phenethylamines are normally taken orally as powder, pills or capsules, or as drops on small slips of paper that are swallowed, but they can also be taken intravenously or inhaled. Effects of phenethylamines include heightened energy, euphoria, elation and openness, as well as altered sensory experiences and hallucinations (4).

In Norway, PMMA has been associated with more than 30 deaths since 2010 (1) – exceeding any other country in Europe. PMMA gives a weaker intoxication effect than amphetamine and methamphetamine and the effects have a slower onset. Intake of a further dose before the effects have set in is the most likely cause of fatal overdoses. This substance is assumed to be far more toxic than MDMA and amphetamine/methamphetamine, also because of the risk of serotonin syndrome (3, 5).

Other phenethylamines can be extremely potent and psychoactive in microgram doses (6, 7).

Synthetic cathinones, so-called bath salts

Synthetic cathinones are substances that are chemically and pharmacologically related to cathinone, the psychoactive ingredient in the leaves of the khat plant, *Chata edulis*. Khat is grown in East Africa and on the Arabian Peninsula and has been used for centuries because of its stimulant effect (8). Some cathinones are sold under false product labelling as bath salts or plant nutrients, others are sold openly as «legal» alternatives to cocaine and methamphetamine (9). Synthetic cathinones have been discovered in seizures sold as cocaine or MDMA (10).

Synthetic cathinones normally occur in powder form, but are also found as pills. The substances are mostly ingested orally, but can also be taken intranasally and rectally (9). They are soluble in water and can be diluted in drinks (11). Intravenous use of synthetic cathinones is increasing in Europe

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MAIN MESSAGE

Novel psychoactive substances are increasingly being discovered and used, and are associated with a high risk of serious and unpredictable effects.

A number of poisonings and deaths have been reported, including in Norway.

Treatment of intoxications and detection of novel psychoactive substances can be a challenge.

There is a need for significantly more research to map the prevalence, mechanisms of action and the extent of injury from the use of novel psychoactive substances.

(1). Reported effects of synthetic cathinones include euphoria, heightened mood, an urge to move, increased sex drive, agitation, clarity of mind and increased loquacity (9).

Mephedrone and methylenedioxypropylvaleron (MDPV) have been the dominant synthetic cathinones on the market, and are internationally associated with an increasing number of emergency hospitalisations (12). No Norwegian studies have investigated this. The effects of these substances on the cardiovascular system are reported to be more potent than those seen after intake of cocaine (13). Other countries report numerous deaths following the use of synthetic cathinones, alone or in combination with other intoxicants (11).

Tryptamines

Tryptamines are derived from the amino acid tryptophan and constitute a heterogeneous group of substances. All of them have hallucinogenic properties, and some have additional stimulant effects (13). LSD belongs to the group of tryptamines and is the most potent hallucinogenic known (13). Tryptamines induce powerful hallucinations with intensified sensory perceptions, euphoria, increased creativity and increased libido, as well as a sense of inner peace (11).

Naturally occurring tryptamines include psilocin/psilocybin, found in psilocybin mushrooms in Norway, and dimethyltryptamine (DMT), which is used in South America in the context of religious ceremonies (9).

Natural tryptamines can be eaten or drunk, for example as tea. Synthetic tryptamines can be taken orally, smoked, sniffed or injected (6). In normal doses their toxicity is low, but deaths have nevertheless been reported from other countries. These are not only attributed to the toxic effects of these substances, but also to their hallucinogenic properties, which may cause fatal accidents (15).

Piperazines

Piperazine has been used since the 1950s for the treatment of intestinal worms, and the substance is not psychoactive in itself (6). However, substances derived from piperazine may be psychoactive. These are frequently sold as pills under the name of ecstasy, as «legal» alternatives to amphetamine and MDMA or with names such as «Legal E» and «Herbal ecstasy». They can be stimulating as well as hallucinogenic, and users describe euphoria and increased self-confidence.

Piperazines are mainly taken orally, but sniffing has also been reported. The effects are unpredictable and may be serious, even after intake of small doses (16). No deaths have been reported as a result of piperazines alone.

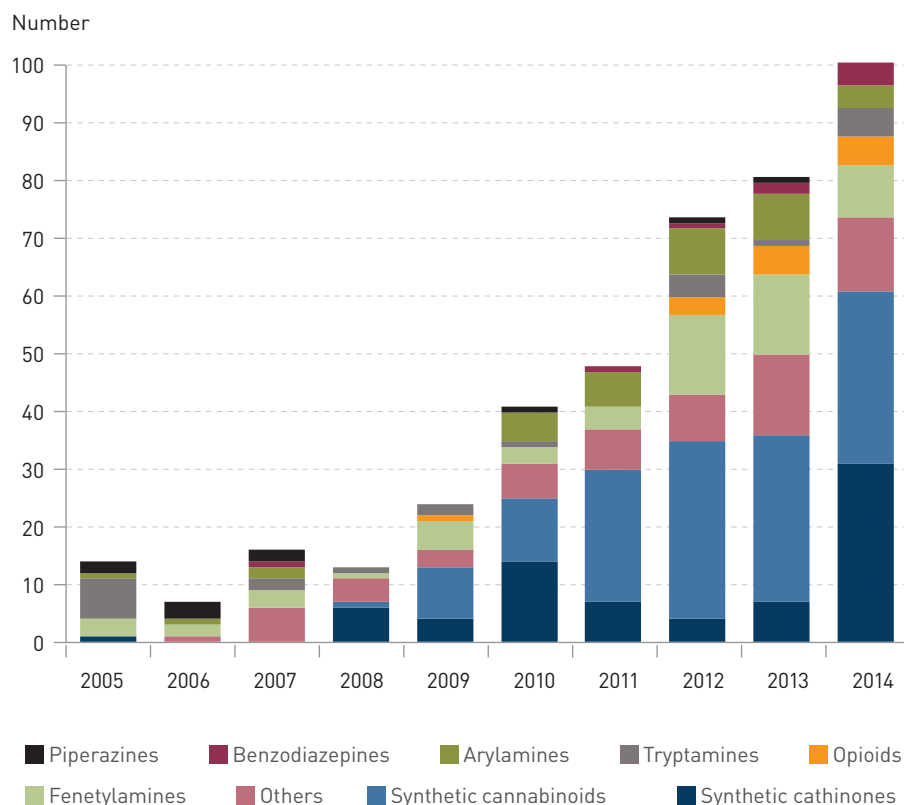


Figure 1 Number and categories of novel psychoactive substances that are reported annually to the EU's early warning system, based on a figure in the organisation's report (1). Reprinted with permission from the European Monitoring Centre for Drugs and Drug Addictions (EMCDDA)

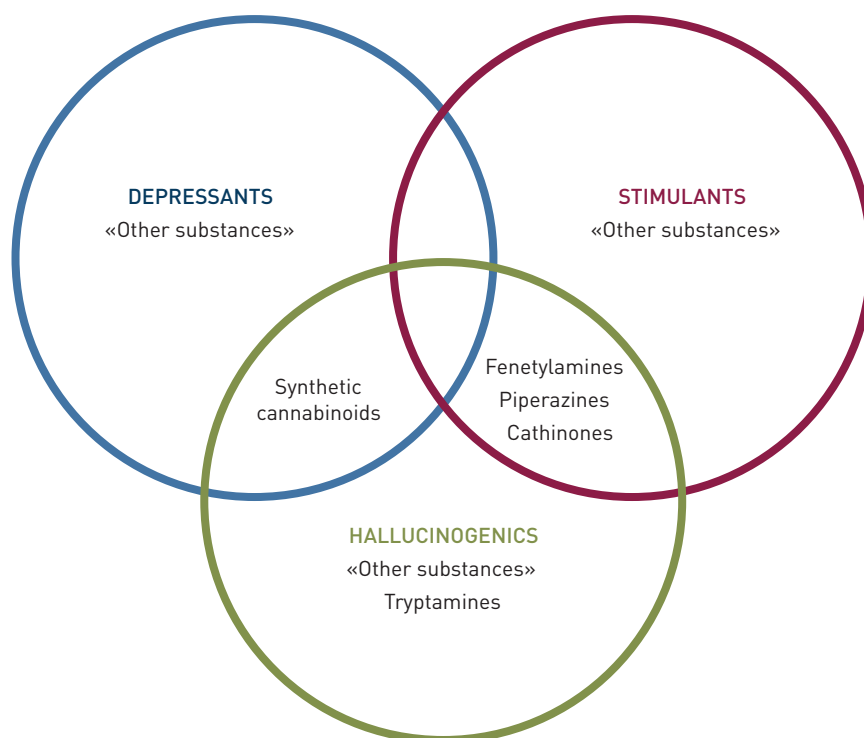


Figure 2 Various main features observed from the use of novel psychoactive substances

Common features of phenethylamines, cathinones, tryptamines and piperazines

Phenethylamines, cathinones, tryptamines and piperazines share a number of mechanisms of action. To a greater or lesser extent, all of them affect the levels of dopamine, noradrenalin and serotonin in the brain's synaptic clefts (9, 10), and most of the substances in these groups have stimulant and/or hallucinogenic effects.

Certain substances, including PMMA and MDMA, have a more pronounced serotonergic effect than the others, and are therefore expected to have more pronounced entactogenic (impact on emotions and communication) and hallucinogenic effects (14). However, substances with a pronounced serotonergic effect are associated with a lower potential for addiction (7).

In cases of overdose, the clinical picture is similar to that for overdoses of traditional central nervous system stimulants such as amphetamine and methamphetamine – hypertension, tachycardia, chest pain, agitation and hallucinations are common (7, 9).

Synthetic cannabinoids

The effects of synthetic cannabinoids are similar to those of tetrahydrocannabinol (THC), the main psychoactive ingredient in cannabis. In common with THC, the synthetic cannabinoids produce their main effects through cannabinoid receptors. Synthetic cannabinoids can be significantly more potent than the active ingredient in cannabis, with a higher risk of adverse effects, including cardiovascular effects, as well as psychosis, seizures and coma.

Most of the deaths reported were caused by effects such as impaired judgement, increased aggression, psychoses and anxiety, which may cause accidents, suicides and outbursts of violence, but deaths by poisoning have also been reported, including in Norway (6, 17). Cardiac ischemia associated with the use of these substances have also been reported (9).

«Other substances»

In the present article, this category encompasses a number of different substances that cannot be classified in any of the other groups. Substances in this group can produce sedative, hallucinogenic and/or stimulant effects (Figure 2). One example is AH-7921, an opioid developed in the 1970s with approximately the same potency as morphine. AH-7921 was detected in connection with two deaths in Norway during the last year (6).

A number of highly potent fentanyl derivatives have also appeared on the illegal

market in recent years and have caused a number of deaths (1). New benzodiazepines are also traded on the illegal market, for example phenazepam, etizolam and diclazepam (1). All of these have been detected in samples in Norway.

Methiopropamine was the most prevalent new psychoactive substance found in samples from cases of driving under the influence of drugs (DUID) in Norway in 2014. This substance has effects similar to those of methamphetamine (18). Its toxicity is unknown, but deaths have been reported.

Treatment of intoxications

For most of the novel psychoactive substances there is no antidote available. Treatment of acute intoxications is therefore symptomatic. However, because of the diversity of the new substances, intoxications may manifest themselves in various ways. For the central nervous system stimulants, undesired effects may include hypertension, tachycardia and arrhythmias. This may cause chest pain, cardiac infarctions and strokes. Such substances may also cause agitation, anxiety and confusion (6, 9).

Treatment of hallucinosis and psychosis caused by these substances requires specialist care, but in acute cases benzodiazepines are frequently used. Seizures and respiratory depression have been described as a result of intake of novel psychoactive substances, some of which may cause vasospasms with subsequent tissue injury of the arms and legs (6, 7, 9). Other studies have described renal failure, hepatic failure, hypokalemia and hyperglycemia (7, 9). Serious and fatal poisonings may also manifest themselves as serotonin syndrome, hyperthermia, cardiac infarction and cerebral oedema. Other manifestations reported after intake of novel psychoactive substances include metabolic acidosis, rhabdomyolysis and disseminated intravascular coagulation (DIC) (6, 9).

Intoxications from synthetic opioids and benzodiazepines may cause symptoms similar to poisonings caused by the traditional substances within the same group. For intoxications from synthetic opioids such as MT-45 as well as several potent fentanyl analogues, the opioid receptor antagonist naloxone has in some cases been shown to reverse the symptoms (6, 19). In light of the pharmacological mechanisms of action of benzodiazepines in general, one may assume that flumazenil has an effect on intoxications caused by novel designer benzodiazepines. Many of the designer benzodiazepines have a long half-life, and repeated doses of the antidote may be required.

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References

1. European Monitoring Centre for Drugs and Drug Addictions (EMCDDA). Europeisk narkotikarapport. Trender og utviklinger. Report No 2015. www.emcdda.europa.eu/attachements.cfm/att_239505_NO_TDAT15001NON.pdf [29.3.2016].
2. Tuv SS, Krabseth HM, Strand MC et al. Nye rusmidler rett fra nett. Tidsskr Nor Lægeforen 2016; 136: 721–3.
3. Al-Samarraie MS, Vevelstad M, Nygaard IL et al. Forgifting med parametoksymetamfetamin. Tidsskr Nor Lægeforen 2013; 133: 966–9.
4. Schifano F, Orsolini L, Duccio Papanti G et al. Novel psychoactive substances of interest for psychiatry. World Psychiatry 2015; 14: 15–26.

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5. Vevelstad M, Øiestad EL, Middelkoop G et al. The PMMA epidemic in Norway: comparison of fatal and non-fatal intoxications. *Forensic Sci Int* 2012; 219: 151–7.
6. Bretteville-Jensen A, Bilgrei O. Nye psykoaktive stoffer – en rusmiddelrevolusjon? Oslo: Universitetsforlaget, 2015.
7. Liechti M. Novel psychoactive substances (designer drugs): overview and pharmacology of modulators of monoamine signaling. *Swiss Med Wkly* 2015; 145: w14043.
8. Al-Samarraie M, Khiabani HZ, Opdal MS. Khat – et nytt rusmiddel i Norge. *Tidsskr Nor Lægeforen* 2007; 127: 574–6.
9. Hohmann N, Mikus G, Czock D. Effects and risks associated with novel psychoactive substances: mislabeling and sale as bath salts, spice, and research chemicals. *Dtsch Arztebl Int* 2014; 111: 139–47.
10. Capriola M. Synthetic cathinone abuse. *Clin Pharmacol* 2013; 5: 109–15.
11. Dargan P, Wood D. Novel psychoactive substances: classification, pharmacology and toxicology. Cambridge, MA: Academic Press, 2013.
12. Hill SL, Thomas SH. Clinical toxicology of newer recreational drugs. *Clin Toxicol (Phila)* 2011; 49: 705–19.
13. Baumann MH, Partilla JS, Lehner KR et al. Powerful cocaine-like actions of 3,4-methylenedioxy-pyrovalerone (MDPV), a principal constituent of psychoactive 'bath salts' products. *Neuropsychopharmacology* 2013; 38: 552–62.
14. Nichols DE. Hallucinogens. *Pharmacol Ther* 2004; 101: 131–81.
15. Corkery JM, Durkin E, Elliott S et al. The recreational tryptamine 5-MeO-DALT (N,N-diallyl-5-methoxytryptamine): a brief review. *Prog Neuropsychopharmacol Biol Psychiatry* 2012; 39: 259–62.
16. Gee P, Gilbert M, Richardson S et al. Toxicity from the recreational use of 1-benzylpiperazine. *Clin Toxicol (Phila)* 2008; 46: 802–7.
17. Westin AA, Frost J, Brede WR et al. Sudden cardiac death following use of the synthetic cannabinoid MDMB-CHMICA. *J Anal Toxicol* 2016; 40: 86–7.
18. Tuv SS, Bergh MS, Vindenes V et al. Methiopropamine in blood samples from drivers suspected of being under the influence of drugs. *Traffic Inj Prev* 2016; 17: 1–4.
19. Bäckberg M, Beck O, Jönsson KH et al. Opioid intoxications involving butyrfentanyl, 4-fluorobutyrfentanyl, and fentanyl from the Swedish STRIDA project. *Clin Toxicol (Phila)* 2015; 53: 609–17.

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