

The misuse of synthetic opioids: harms and clinical management of fentanyl, fentanyl analogues and other novel synthetic opioids

Information for clinicians

Dima Abdulrahim and Owen Bowden-Jones
on behalf of the NEPTUNE group

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Club Drug Clinic/Central and North West London NHS Foundation Trust (CNWL)

69 Warwick Road

Earls Court

London

SW5 9HB

<http://www.Neptune-clinical-guidance.co.uk>

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Section 1. Introduction

Document aims

Synthetic opioids, including fentanyl, are important therapeutic medicines that are used widely for pain, as well as for anaesthesia, in combination with other medication. This document focuses on the misuse of fentanyl, fentanyl analogues* and other novel synthetic opioids and does not address issues pertaining to their use in legitimate therapeutic and clinical contexts. Specifically, this document focuses on the clinical management of the health-related harms associated with the misuse of these substances, both acute harms as well as harms from frequent and long-term use (chronic harms). It is aimed primarily at a clinical audience.

Although there is a large body of evidence on pharmaceutical synthetic opioids and fentanyl and its analogues, the evidence on the novel fentanyls and other novel opioids, their harms and management, is currently limited and cannot be considered as robust. Nonetheless, the research findings are broadly consistent and this document provides clinically relevant information based on the best evidence currently available.

Misuse of synthetic opioids

Although fentanyl, fentanyl analogues and other synthetic opioids play an important and well documented therapeutic role, their misuse, especially in high doses, can lead to acute toxicity and life-threatening adverse effects.¹ Fentanyl and other synthetic opioids also have a high liability to misuse and chronic adverse effects, including dependence.

The misuse of fentanyl and other synthetic opioids is not a recent phenomenon. In the 1970s and 1980s, products containing fentanyl and its analogues appeared on the illicit drug market, and were associated with accidental overdoses.^{2,3} Today, in some parts of the world novel synthetic opioids are once again associated with an overdose epidemic.⁴ It has been noted by Rudd et al. that as the numbers of deaths from natural and semi-synthetic opiates were stabilising in the US over the period 2010–15, deaths from synthetic opioids and illicitly manufactured fentanyls were rising at an alarming rate.⁵

Geographical patterns of use

There are geographical differences in the aetiology and extent of the crisis. In North America, the significant increase in the misuse of synthetic opioids and overdose-related

* For the sake of convenience, this document will sometimes use the generic term of 'fentanyls' to refer to fentanyl and its analogues.

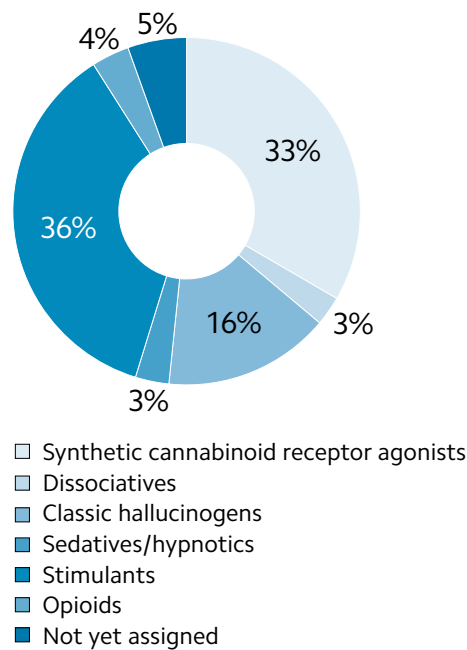


Figure 1. Proportion of NPS by pharmacological effect (December 2016)

Source: United Nations Office on Drugs and Crime (UNODC), World Drug Report 2017

deaths was initially associated with addiction to legitimately prescribed opioid pain medicines. At the moment, dependence on prescription opioids does not appear to have played a significant role in its illicit/non-medical use in Europe (including the UK), as it has in North America,⁶ although the possibility of under-reporting cannot be dismissed.⁷

What Europe, including the UK, shares with the US and Canada is the recent emergence of novel highly potent synthetic opioids, in particular fentanyl derivatives and other substances, that are linked with significant risk of acute toxicity and overdose. Although the number of novel synthetic opioid analogues detected is small in comparison with other types of novel psychoactive substance (NPS), such as stimulants, the largest percentage increase in recent years has been observed in the synthetic opioids.

At a global level, synthetic opioids represented 4 per cent of all NPS at the end of December 2016, as shown in Figure 1, as opposed to only 2 per cent at the end of 2014.⁸ Between 2012 and 2016, 17 novel fentanyl analogues were reported to the United Nations Office on Drugs and Crime (UNODC) Early Warning Advisory from countries in East Asia, Europe and North America.*³ These are usually manufactured in clandestine laboratories and are referred to as non-pharmaceutical fentanyls (NPFs).

Similarly, 25 novel opioids have been detected on Europe's drug market since 2009, including 9 reported for the first time in 2016. These include 18 fentanyls, 8 of which

* New fentanyls reported: 3-fluorofentanyl; 4-fluorobutyrfentanyl; 4-methoxybutyrfentanyl; acetylfentanyl; acrylfentanyl; beta-hydroxy-thiofentanyl; butyrfentanyl; despropionylfentanyl; despropionyl-2-fluorofentanyl; furanylfentanyl; isobutyrfentanyl; (iso)butyr-F-fentanyl N-benzyl analogue; methoxy-acetylfentanyl; ocfentanil; para-fluoroisobutyrfentanyl; tetrahydrofuranylfentanyl; valerylfentanyl.

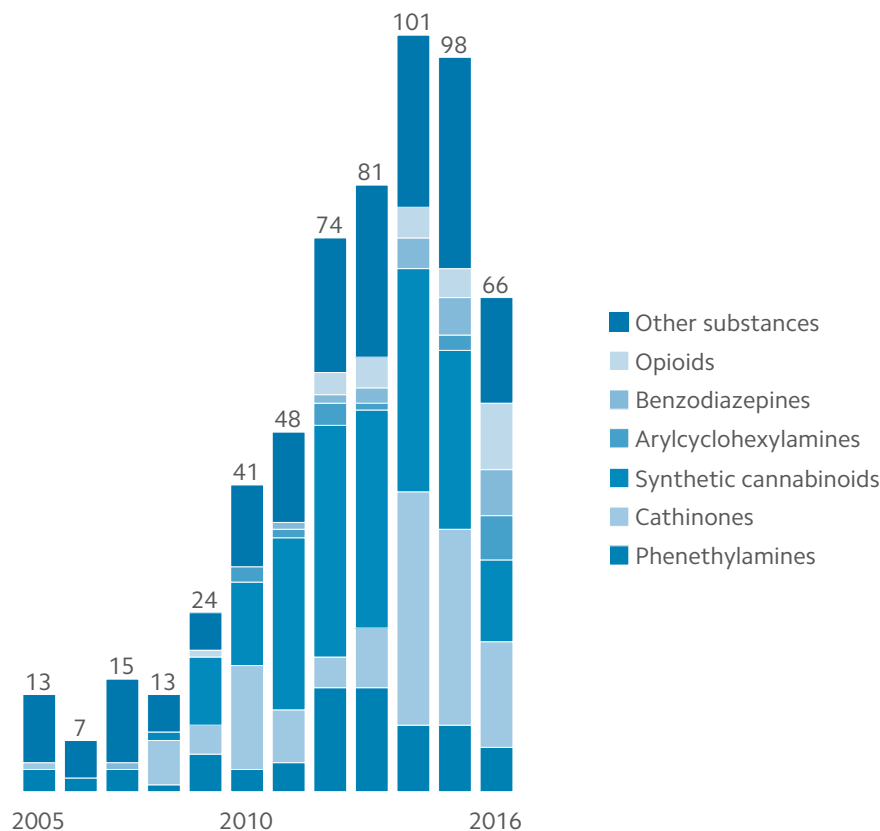


Figure 2. Number and categories of new psychoactive substances notified to the EU Early Warning System for the first time, 2005–16

Source: EMCDDA- European Drug Report 2017

were reported for the first time in 2016.⁷ The increase in opioid NPS detected in recent years is shown in Figure 2.

For individuals and criminal organisations involved in the illicit drug trade, fentanyl offers a number of ‘advantages’ over the established opioid, heroin. Fentanyls have greater potency, resulting in less bulk and weight to transport and distribute than is the case with heroin. Fentanyls can be manufactured reliably and in large quantities from abundant chemical precursors, whereas heroin requires an opium crop, which must be produced in the open air.³ The low production cost and wholesale cost of fentanyl in comparison with heroin has been identified as a reason for the recent increase in fentanyl on illicit markets. In 2017, for example, the reported wholesale cost of heroin was approximately \$65,000 per kilogram, whereas fentanyl was available at roughly \$3,500 per kilogram.⁹

The numbers of heroin- and fentanyl-related overdoses are rising worldwide,¹⁰ with very large numbers of deaths reported in the US and Canada, as discussed below. Although this situation is not reflected in Europe, some fatalities associated with these substances have been reported in mainland Europe and in the UK but, at present, synthetic opioids, including fentanyls, used for non-medical purposes in the UK can be described as ‘low use but high risk/harm’ substances. Vigilance is required,

as well as improved confidence and competence in the identification, assessment and management of their harms in clinical practice.

Legal status in the UK

In the UK, fentanyl is classified as a controlled Class A drug under the Misuse of Drugs Act 1971. Almost all novel fentanyls are covered by the UK's generic control (Class A) but UK control of precursors is (currently) governed by EU regulations, as it is classed as a trade issue. The fentanyl precursors NPP and ANPP were due to be controlled in the UK under the EU regulations in 2018.

The synthetic opioids AH-7921, MT-45 and U-47700 are Class A drugs under the Misuse of Drugs Act 1971. All other psychoactive substances not currently covered by that Act now fall under the Psychoactive Substances Act 2016.

Section 2. Fentanyl and fentanyl derivatives and analogues

Pharmacology

Fentanyl (N-[1-(2-phenylethyl)-4-piperidinyl]-N-phenylpropanamide) is a potent opioid used in human and veterinary medicine. It has analgesic and sedative effects and is widely used in the management of severe pain and in anaesthesia.³ Fentanyl is a full agonist at the μ -opioid receptor. It is at least 80 times more potent than morphine^{11,12} and when misused is associated with a risk of acute toxicity. Carfentanyl is intended only for veterinary use on large animals, and is not approved for medical use in humans; it is estimated to be about 10,000 times more potent than morphine.^{3,13,14}

Fentanyl derivatives sold on the illicit market include analogues that have been rediscovered by the manufacturers from studies described in the scientific literature but never developed into pharmaceutical products.* There are also newly designed fentanyl analogues made by new modifications of the fentanyl chemical structure, to avoid legal control, as with other NPS. They are sometimes referred to as non-pharmaceutical fentanyls (NPF) and include:

- furanylfentanyl, or N-phenyl-N-[1-(2-phenylethyl)piperidin-4-yl]furan-2-carboxamide;
- acrylylfentanyl, or N-(1-phenethylpiperidin-4-yl)-N-phenylacrylamide;
- acrylofentanyl, or N-(1-phenethylpiperidin-4-yl)-N-phenylacrylamide;
- *para*-fluoroisobutyrfentanyl;
- 4-fluorobutyrfentanyl.

Fentanyl has a rapid onset of action, almost immediate following intravenous administration, but its maximal analgesic and respiratory depressant effect may not be noted for several minutes. Following intramuscular administration, the onset of action is from 7–8 minutes and the duration of action is 1–2 hours. The duration of action of fentanyl, when administered intravenously, is 30–60 minutes,^{15,16} much shorter than with heroin (4–5 hours). This may lead to frequent redosing.¹⁷

Overall, reasons for the potency of fentanyl include its high lipophilicity (which allows it easily to cross the blood–brain barrier) and high receptor affinity, with high selectivity and specificity for the μ -opioid receptor over other opioid receptor subtypes.¹⁸ In terms of toxicity, as potent agonists of the μ -opioid receptor, fentanyls are associated with a number of acute physiological effects, including respiratory depression.

* Examples include acetylfentanyl, butyrfentanyl, furanylfentanyl (N-phenyl-N-[1-(2-phenylethyl)piperidin-4-yl]furan-2-carboxamide) and ocfentanil.

Previously developed fentanyl analogues have properties similar to fentanyl,* but current knowledge of novel non-pharmaceutical analogues is limited and these drugs may differ in their potency, efficacy and duration of action.^{19,20}

The misuse of fentanyls is associated with a high risk of acute toxicity, or ability to cause harm through a single or short-term exposure to the drug. For fentanyl, the estimated lethal dose in humans could be as low as 2 mg by intravenous injection. Information on the effect of the novel non-pharmaceutical fentanyls, especially in humans, is currently very limited. Nonetheless, in vitro studies have established that furanylfentanyl is a potent agonist of the μ -opioid receptor. Cases of acute intoxication suspected to be due to furanylfentanyl reported in Europe showed clinical features generally consistent with opioid-like toxicity and included life-threatening effects; toxicological data on these deaths where furanylfentanyl was detected suggest that the drug was the cause of death or was likely to have contributed to death (even in presence of other substances).^{21,22} Similarly, although the acute toxicity of acryloylfentanyl in humans has not been determined, observations from a study conducted in mice suggest that it is similar to that of fentanyl, with considerable risk of acute toxicity through respiratory depression;²³ moreover, cases of acute toxicity associated with acryloylfentanyl have been reported in Swedish studies.²⁴

Markets

Fentanyls destined for the illicit market appear to come from both:

- diversion of fentanyl-containing medicines from the regulated supply chain,²⁵ (significant in some parts of the world but which does not appear to be significant in the UK at the present time), and
- illicit production in clandestine laboratories of non-pharmaceutical fentanyls.

* Examples of fentanyls that have not been approved for medical use, are listed below:

- acetylfentanyl (N-phenyl-N-[1-(2-phenylethyl)piperidin-4-yl] acetamide; acetyl fentanyl, desmethyl fentanyl, MCV 4848, NIH 10485);
- acryloylfentanyl (N-phenyl-N-[1-(2-phenylethyl)piperidin-4-yl] prop-2-enamide, acrylfentanyl, acryloyl-F, Acr-F, ACF);
- alpha-methylfentanyl (N-phenyl-N-[1-(1-phenyl-2-propanyl) piperidin-4-yl] propanamide);
- 3-methylfentanyl (N-[3-methyl-1-(2-phenylethyl)piperidin-4-yl]-N-phenylpropanamide, mefentanyl, 3-MF);
- butyrylfentanyl (N-phenyl-N-[1-(2-phenylethyl)piperidin-4-yl]butanamide, butyl fentanyl, BF);
- 4-methoxybutyrylfentanyl (N-(4-methoxyphenyl)-N-[1-(2-phenylethyl)piperidin-4-yl]butanamide, 4-MeO-BF);
- 4-fluorobutyrylfentanyl (N-(4-fluorophenyl)-N-[1-(2-phenylethyl)piperidin-4-yl]butanamide, 4-FBF);
- 4-fluoroisobutyrylfentanyl (N-(4-fluorophenyl)-2-methyl-N-[1-(2-phenylethyl)piperidin-4-yl] propanamide, 4F-iBF);
- 4-chloroisobutyrylfentanyl (N-(4-chlorophenyl)-2-methyl-N-[1-(2-phenylethyl)piperidin-4-yl] propanamide, 4F-iBF);
- furanylfentanyl (N-phenyl-N-[1-(2-phenylethyl)piperidin-4-yl]-2-furancarboxamide, furafentanyl);
- cyclopentylfentanyl (N-(1-phenylethyl)piperidin-4-yl)-N-phenylcyclopentanecarboxamide, CP-F);
- tetrahydrofuranylfentanyl (N-(1-phenethyl)piperidin-4-yl)-N-phenyltetrahydrofuran-2-carboxamide, tetrahydrofuranfentanyl, THF-F);
- ocfentanil (N-(2-fluorophenyl)-2-methoxy-N-[1-(2-phenylethyl)piperidin-4-yl]acetamide, ocfentanil, A-3217).

Synthetic opioids used for non-medical purposes, including fentanyl and its analogues, are sold online, typically on the 'darknet',²⁶ as well as by dealers in the illicit market.

Mode of use

Fentanyl and its salts are typically white granular or crystalline powders. Clandestinely manufactured fentanyl or its analogues are sold in solid or liquid forms,³ including powders, pills, capsules, patches, lozenges and liquid and on blotting paper. Although less common, furanylfentanyl has also been seized in Europe as a green 'herbal' material, as well as being sold as e-liquids for vaping in electronic cigarettes.²¹

Fentanyl and its analogues may be consumed by several routes, including injecting (intravenous or intramuscular), orally, transdermally, by smoking,²⁷ intra-nasally or sublingually through a spray or vaporisation.²¹ Also worth noting are new forms of pharmaceutical fentanyl, for example for oromucosal administration as 'lollipops'.

One concern noted in the EMCDDA *European Drug Report 2017* was the appearance on the market of nasal sprays containing non-pharmaceutical fentanyls, such as acrylylfentanyl and furanylfentanyl.⁷

In the UK at the current time, fentanyl, fentanyl analogues and other new synthetic opioids are mainly sold on the illicit market as heroin or mixed with heroin to people who believe they are receiving heroin. There are in addition reports from elsewhere in the world that they are also sold as, or mixed with, other illicit drugs and counterfeit medicines.⁷

International evidence suggests that fentanyl products have also been found in products sold as cocaine, or crack cocaine, 'black tar' heroin and MDMA.^{3,28} Furthermore, there are reports of individuals purchasing prescription medication, such as oxycodone⁹ and alprazolam (Xanax),^{29,30} on the internet only to be sold counterfeit products that contain new fentanyls.^{31,32}

Diverted pharmaceutical fentanyl does not seem to be a significant problem in the UK at this time. In some countries, however, fentanyl has been reported to be diverted from pharmaceutical products, mostly extracted from transdermal patches, and to a lesser extent lozenges, sublingual tablets and solutions of fentanyl intended for infusion.

In addition to diverted fentanyl products, even 'exhausted' medical transdermal patches will still contain significant amounts of fentanyl when removed and so need to be disposed of responsibly.

Fentanyl transdermal patches can be misused in a variety of ways, including:

- extraction of gel for injection or ingestion;
- heating the patch in a glass container and inhaling the fentanyl emitted;

* The darknet is an encrypted part of the internet, sometimes also referred to as cryptomarkets. They provide a largely anonymous platform for trading in illicit goods and services, with drugs estimated to account for around two-thirds of darknet market activity.

- smoking on foil;
- using on the skin;
- cutting into pieces and sucking or swallowing;
- inhalation via a vaporiser.

There are also reports of patches being simmered in a small volume of water and the solution obtained injected intravenously; and of frozen patches being cut into pieces and then placed under the tongue or in the cheek cavity for drug absorption, or inserted into the rectum.^{9,20,25,27,33,34,35,36,37,38,39}

Desired effects of fentanyls

The effects of fentanyls that are desired by those who use them outside medical supervision are similar to those of other opioids and include analgesia, anxiolysis, euphoria, drowsiness and feelings of relaxation, with some suggestion that the latter are less pronounced than with heroin and morphine.^{40,41}

There are reports of heroin users being suspicious that they had unknowingly consumed a new synthetic opioid, as their experience of the drug effect was different from normal.⁴² Some research suggests that users who were unaware that they had used a fentanyl (initially believing that they were administering heroin) described the effects of fentanyls as stronger and qualitatively different from those of heroin,⁴³ or describe the experience as like taking heroin but more intense.^{44,45,46}

Unwanted effects of fentanyls

Studies have shown that a substantial number of people who had used fentanyl did not know that they had done so when they consumed the drug, but thought they were using heroin or another substance.⁴⁴ This can result in a user inadvertently consuming a significantly more potent and more unpredictable substance than intended.^{3,31} In addition to the risks associated with the potency of fentanyl and its analogues, fentanyl products sold online and on the black market pose a threat to public health, not least because of variable components and erratic adulteration.^{3,17} For example, in a study of fentanyl injecting in Toronto, people who used the drug reported that the potency of the substance was unpredictable.⁴⁷

The use of fentanyls can be also associated with dysphoria, depression, paranoia and hallucinations. Adverse effects of fentanyl include constipation, nausea, vomiting, itching, cough suppression, nasal burn or nasal drip after insufflation, a bitter taste after oral ingestion, anxiety, agitation, sweating, disorientation, orthostatic (or postural) hypotension and urinary urgency or retention.^{41,48,49}

The risk of overdose is increased by unsafe methods of preparation and administration (especially intravenous injection), imprecise measuring by users, drug potency and users mostly being unaware of what they are consuming.³ As with other drugs

sold on the illicit market, they may not contain what is claimed on the packaging. For example, a study from Sweden found that NPS products sold as the fentanyl analogue butyrfentanyl (butyrylfentanyl) instead mainly contained the more potent fentanyl.⁵⁰

Acute adverse effects of fentanyl and its analogues

The reported acute harms associated with the use of fentanyls are summarised in Table 1.

Table 1. Commonly reported features of fentanyl toxicity

Fentanyl toxicity	Fentanyl severe toxicity	Differences between heroin and fentanyl overdoses
<ul style="list-style-type: none"> • Miosis (pinpoint pupils) • Nausea, vomiting • Anxiety, agitation • Euphoria, dysphoria • Depression • Paranoia • Hallucinations 	<ul style="list-style-type: none"> • Respiratory and central nervous system depression • Decreased consciousness • Apnoea • Can lead to deep coma, convulsions and respiratory arrest. • Sudden-onset chest wall rigidity may be associated with increased risk of mortality 	<p>In comparison with heroin, intoxication with fentanyl and analogues presents with:</p> <ul style="list-style-type: none"> • increased risk of overdose • more rapid onset of overdose • more rapid progression of signs and symptoms

As with most other opioids, fentanyl intoxication is linked to miosis (pinpoint pupils). However, miosis is not always a reliable clinical sign of toxicity for all opioids, as some have miosis absent from their toxicity profile.

Fentanyl and its derivatives are associated with decreased consciousness and a high risk of respiratory depression and overdose.^{51,52,53} Fentanyl causes dose-dependent respiratory depression, which has been reported by one study to be maximal 25 minutes after a single intravenous dose and to last as long as 2–3 hours.⁴⁸ Fentanyls can also be linked to apnoea, severe bradycardia, asystole, convulsions, respiratory arrest, deep coma and death.⁵⁴

Fentanyl toxicity has been associated with chest wall rigidity, particularly when injected.^{40,41,48,49} There are suggestions that sudden-onset chest wall rigidity is a significant factor in deaths from intravenous fentanyl use.⁵⁵

Uncommon features of toxicity

Uncommon or rare symptoms described by case reports in the literature include:

- immediate blue discolouration of the lips, gurgling sounds with breathing, stiffening of the body or seizure-like activity, foaming at the mouth, and confusion or strange affect before unresponsiveness;⁵⁶

- lung damage, including alveolar haemorrhage, haemoptysis and acute lung injury, with butyrfentanyl;⁵⁷
- toxic leukoencephalopathy characterised by cerebellar white matter;⁵⁸
- syncope and chest pain mimicking acute coronary syndrome;⁵⁹
- unusual amnestic syndrome associated with combined fentanyl and cocaine use that included acute, complete and bilateral hippocampal lesions on magnetic resonance imaging.⁶⁰

Differences between heroin and fentanyl acute toxicity

The high potency of fentanyls, as well as their rapid onset of action, contributes to making them in a non-clinical context particularly dangerous in comparison with heroin.^{12,50,61} A report from a drug consumption room in Australia found that, under medical surveillance, the risk of overdose when injecting fentanyl was two times higher than when injecting heroin, and eight times higher than when injecting other prescription opioids.⁶²

There are differences between fentanyl and heroin overdoses. Fentanyl overdose can begin suddenly, rapidly progress to death and manifest atypical physical symptoms. In comparison with heroin overdose, where death typically does not occur until at least 20–30 minutes after use,⁶³ fentanyl can be associated with potentially lethal respiratory depression within 2 minutes.^{17,30}

Fatalities associated with fentanyl often also involve the concurrent use of other substances, such as cocaine and heroin.^{2,64,65} The use of fentanyl (and analogues) at the same time as other CNS depressants (e.g. alcohol, benzodiazepine, pregabalin, gabapentin) can have serious adverse effects; poly-drug use has been reported to be common among fentanyl-related fatalities in Europe²¹ and elsewhere.³⁴

Injecting is the most commonly reported route of administration of fentanyl in fatal overdoses, but deaths linked with other modes of use of fentanyl have also been reported. For example, a study looking at fentanyl-related deaths in the US from July to December 2016 reported that one in five deaths involving fentanyl or fentanyl analogues had evidence of insufflation, smoking or ingestion and no evidence of injecting.⁶⁶ This is an important distinction from heroin, whereby deaths are most likely to be associated with intravenous injecting.

Fentanyl-related deaths

The non-medical use of fentanyl has recently been implicated in a significant and increasing number of deaths in several countries, including some European countries, Australia and Japan.^{40,67,68,69,70} In Canada and the US, the problem of opioid-related overdose death has particularly severe for a number of years.^{5,71,72,73,74}

There is a debate over the true extent of fentanyl deaths in the US, but the Center for Disease Control and Prevention (CDC) reports that the death rate from the use of synthetic opioids other than methadone, and which includes drugs such as tramadol and fentanyl, increased by 72.2% from 2014 to 2015. According the Center, recent state reports have indicated that increases in the numbers of deaths involving synthetic opioids have been associated with drug products testing positive for fentanyl, but not fentanyl prescribing rates. The suggestion is that the increases in the numbers of deaths involving synthetic opioids are being driven by increases in the numbers of deaths involving fentanyl, which are likely due to illicitly manufactured fentanyl.⁷⁵ Provisional data published on the CDC website suggest an increase from 9,945 deaths in 2016 associated with synthetic opioids (excluding methadone) to 20,145 from 1 January 2017 to 8 June 2017.⁷⁶

Deaths related to synthetic opioids, including fentanyls, have been reported in Europe, albeit at a significantly lower rate. During 2016, the EMCDDA and Europol launched special investigations into acryloylfentanyl and furanylfentanyl, after signals were detected through the EU Early Warning System. More than 50 deaths were reported, many of which were attributed directly to these substances. In addition, the EMCDDA also issued five alerts to its network across Europe related to these and other new fentanyls.^{70,77}

In the UK, data from the Office for National Statistics suggest that deaths associated with fentanyl and its analogues are increasing, as can be seen in Figure 3. It is possible that increased vigilance on the potential implication of fentanyl compounds in opioid overdose death will increase detection.

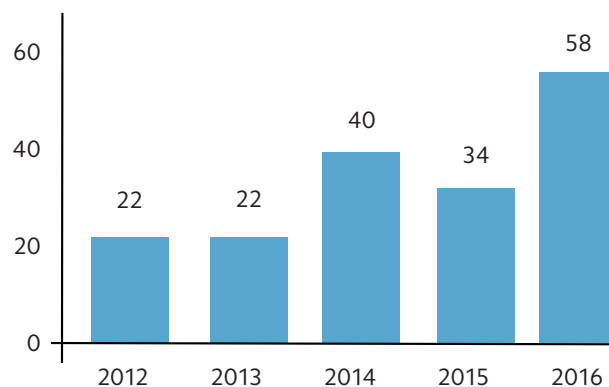


Figure 3. Number of fentanyl-related deaths, where selected substances were mentioned on the death certificate, deaths registered in England and Wales, 2012–2016⁷⁸

According to the UK National Crime Agency, it is possible that the number of deaths attributed to fentanyl will rise further, due to the time lag in toxicology results, and because of back testing of toxicological samples originally not tested for fentanyl.⁷⁹ It was reported in July 2017 that exposure to carfentanyl had been analytically confirmed in 29 deaths in the UK, 28 of which occurred between February and May 2017.⁸⁰ However, many of these deaths also involved heroin and it is difficult to assess accurately the significance of the presence of fentanyl.

A study of 25 fatalities in the north of England associated with fentanyl and fentanyl derivatives reported that the majority were men, with a history of heroin use, aged from 21 to 54 years.⁸¹

Poly-drug use

As with other opioids, the combined use of fentanyl with other CNS and respiratory depressants, such as alcohol or benzodiazepines, is linked to increased toxicity. Studies have recommended the ongoing need for targeted messages on risks of synthetic opioids alone, as well as their use in combination with alcohol and other CNS depressants.⁸²

Interactions with other drugs

- The use of fentanyl in combination with inhibitors of the isoenzymes CYP450 3A4 and CYP450 3A5 may result in increased plasma concentration of fentanyl (and probably new analogues), thus increasing the risk of poisoning, including potentially fatal respiratory depression. Inhibitors include ritonavir, clarithromycin, erythromycin, fluconazole, indinavir, itraconazole, ketoconazole, nefazodone, saquinavir, verapamil and grapefruit juice.²¹
- There is limited evidence that use of fentanyl with serotonergic agents (prescribed medication including SSRIs, SNRIs or MAOIs, or illicit substances, such as MDMA) may be associated with serotonin syndrome.⁸³ It is not known if this association is also seen with fentanyl derivatives.²¹
- Buprenorphine is predicted to increase the risk of opioid withdrawal when given with fentanyl.⁸⁴

Other types of exposure to fentanyls

The risks associated with fentanyl and its analogues are not limited to its direct consumption and some professionals may come into contact with them (e.g. border control staff, enforcement officers). Adverse effects may result from handling the drugs without the precautions that prevent the substance from being inhaled or absorbed through the skin or mucous membranes.³ The current official US government safety advice for first responders reinforces the following points:⁸⁵

- Fentanyl can be present in a variety of forms (e.g. powder, tablets, capsules, solutions and rocks).
- Inhalation of airborne powder is most likely to lead to harmful effects, but is less likely to occur than skin contact.
- Incidental skin contact is not expected to lead to harmful effects if the contaminated skin is promptly washed with water.

- Personal protective equipment (PPE) is effective in protecting people from exposure.
- Slow breathing or no breathing, drowsiness or unresponsiveness, and constricted or pinpoint pupils are the specific signs consistent with fentanyl intoxication.
- Naloxone is an effective medication that rapidly reverses the effects of fentanyl.

In the UK, the Home Office Centre for Applied Science and Technology recommends that Border Force staff use personal protective equipment (PPE) when handling unknown bulk NPS compounds.

Fentanyl has also been used as a human incapacitation agent, for example in an incident in a Moscow theatre in October 2002, where it caused the death of a large number of hostages.^{86,87,88,89}

Lack of testing

Analytical methods for detecting fentanyl use are very limited at present and it is unlikely that onsite testing is currently available in hospital laboratories.

Standard immunoassay screening tests in the clinical setting do not detect synthetic opioids. More complex methods are required, such as gas chromatography mass spectrometry or liquid chromatography mass spectrometry. Testing is complicated by the fact that tests for fentanyl may not detect all analogues.

Overdose management

The evidence on the management of acute adverse effects associated with the misuse of fentanyls is limited, but emerging.¹⁷

There are clear distinctions between the responses to overdose carried out in community settings and responses in hospital or other acute medical settings.

In community settings

As part of a drive to reduce the number of drug-related deaths in the UK, there has been a widening of the distribution of naloxone, an antidote to overdoses of opioids, including fentanyls. Since 2015, people employed in or otherwise engaged in drug treatment services can supply naloxone that has been obtained by their drug service to others, as long as it is for the purpose of being available to save life in emergency. Although naloxone is a prescription-only medicine, a prescription is not needed for the naloxone to be supplied in this way. There is good evidence that pre-provision of naloxone to heroin users can be helpful in reversing heroin overdoses. There is also evidence for the effectiveness of training family members or peers in how to administer the drug.⁹⁰

Extensive guidance has been issued in the UK on the provision of naloxone for the reversal of opioid overdoses in the community.⁹⁰ The prompt administration of the antidote in emergency situations can reverse respiratory depression and can be

lifesaving, but giving too much can lead to an acute withdrawal syndrome. To that effect, UK Medicines Information (UKMi) recommends that, in community settings, the following should take place for the management of opioid overdose:⁹¹

- An intramuscular dose of 400 µg is given initially, with further 400 µg doses given incrementally every 2–3 minutes until an effect is noted or the ambulance arrives.
- Total available naloxone in a community overdose situation before an ambulance arrives is unlikely to exceed 2 mg (five 400 µg doses), which is the amount at which the BNF recommends the diagnosis of opiate overdose be reviewed.

Until evidence is available to suggest otherwise, this also applies to the reversal of suspected fentanyl overdose.

- It has been suggested that where there is suspicion that fentanyl is implicated, the importance of calling ambulance or emergency services promptly and transfer to hospital should be emphasised, especially in cases where naloxone is not available in the community, or if there is need for prolonged naloxone administration, which may be the case of fentanyl overdose.
- It has also been suggested that more advanced resuscitation skills (such as chest compressions and automatic defibrillators) may need to be more widely incorporated into community emergency response training to tackle fentanyl overdose, and is vital if responsiveness to naloxone administration is inadequate or delayed.¹⁷

There is presently no evidence that higher doses of naloxone should be used in community settings. In the US and Canada, where morbidity and mortality associated with fentanyl misuse is significantly higher than in the UK, a few small-scale interventions targeted at fentanyl have been developed based on the assumption that take-home naloxone kits provided to users of novel synthetic opioids may require higher doses of naloxone than those provided to heroin users.⁹² There are reports of some naloxone programmes providing more than the standard two doses of naloxone, and others have begun utilising higher-dose devices.¹⁷ It is not clear yet whether these approaches will prove to be effective.

There are also some suggestions from North America that naloxone programmes should be adapted to take into account the dynamic opioid problem (and fentanyl and its analogues in particular), including scale-up to new venues and social networks for distribution. There are some suggestions of new standards for post-overdose care, the development of supervised drug consumption services and the integration of new technologies to detect overdose and deliver naloxone.¹⁷ We do not know how effective such interventions would be in reducing fentanyl-related deaths.

In hospital settings

It has been argued NPS opioids, including fentanyls, do not require hospital clinical staff to change their approach to the management of acute opioid toxicity and overdose.⁴

- It has been suggested that initial care of the opioid-intoxicated patient should focus on protecting the airway and maintaining breathing and circulation, as in any emergency. External stimulation should be attempted in all patients, and an external ventilatory support mask device should be provided for those with profound hypoventilation.⁴
- Anticipatory titration of naloxone with the goal of restoring ventilatory drive remains the mainstay for patients who do not respond in a sustained fashion to the above.⁴ Overdoses can be reversed through the use of naloxone as in the case of other opioids, together with appropriate supportive care.⁹³
 - It has been proposed that clinical suspicion may be sufficient to carry out empirical treatment with naloxone, considering that there are no significant side-effects to its use in such circumstances.⁹³
 - Potent, faster-acting synthetic opioids, such as fentanyls, make it more difficult to balance the need for an effective opioid antidote with the risks of precipitated withdrawal.⁹⁴

An alert issued by the UK Department of Health in April 2017⁹⁵ recommended the standard naloxone dosing regime where fentanyl/carfentanyl overdose is suspected (for adults and children aged over 12 years) for use in acute hospitals, subject to clinical assessment of the individual case:

- Give an initial dose of 400 µg (0.4 mg) intravenously.
- If there is no response after 60 seconds, give a further 800 µg (0.8 mg).
- If there is still no response after another 60 seconds, give another 800 µg (0.8 mg).
- If there is still no response, give a further 2 mg dose. Large doses (4 mg) may be required in a seriously poisoned patient.
- Aim for reversal of respiratory depression, not full reversal of consciousness.

There are reports of multiple doses of naloxone sometimes being required.⁵⁶ Because the length of time between substance use and potentially life-threatening respiratory depression is shorter with fentanyl than with heroin, the reversal of the fentanyl overdose may be less likely than with heroin. There have been reports of unsuccessful attempts to revive with naloxone despite administration of multiple or escalating doses. Despite the standard resuscitation procedures indicating the potential need to administer repeat doses of naloxone, the clinical outcome of fentanyl poisoning may vary from case to case.⁹⁶

In comparison with heroin overdose

There are other differences between the management of heroin overdoses and those related to fentanyls.

- In cases of fentanyl overdose, it seems that more rapid administration, and perhaps escalation, of additional doses of naloxone is needed in comparison with overdoses of heroin or other opioids.

- In cases of heroin overdose, some have suggested that patients with heroin-induced respiratory depression can be safely discharged from hospital after a one-hour observation period.⁹⁷ Armenian et al. argued that this is *not* recommended for synthetic opioids, including fentanyls, which require larger and repeated doses of naloxone and require a longer period of observation because symptoms may recur when the naloxone wears off.¹⁸
- They also recommend that due to the extremely high potency and lack of human pharmacokinetic and clinical overdose knowledge of carfentanyl, that all carfentanyl cases be monitored for 24 hours in the hospital setting.¹⁸

Differences between the management of overdoses caused by heroin and fentanyls

The broad principles of management apply to all opioids, with the following to be taken into account where fentanyl is suspected:

- Where the use of fentanyls is suspected, there is a need to call emergency services and transfer to hospital, especially in cases where naloxone is not available in the community, or if there is need for prolonged naloxone administration.
- A more rapid escalation of additional doses of naloxone may be needed in comparison with heroin or other opioids.
- Overall, higher doses of naloxone may be needed for fentanyl patients than for heroin patients.
- A longer period of observation is advised for fentanyl patients than for heroin patients.
- It has been recommended that all cases of overdose with carfentanyl, due to its extremely high potency, be monitored for 24 hours in the hospital setting.

Chronic effects and dependence

Despite limited evidence, it is assumed that fentanyls, including the novel analogues, have a high potential for harmful use and a high dependence liability that is similar to, or greater than, that with morphine.

Increasing numbers of people are entering drug treatment for fentanyl-related harmful or dependent use. In the US, where there is currently a significantly higher level of fentanyl use than in the UK, a study of people entering drug treatment reported that fentanyl misuse increased modestly from 2012 to 2016. However, it also showed that whereas the misuse of branded fentanyl products remained stable, the misuse of 'unknown' fentanyls, presumed to be non-pharmaceutical fentanyl, increased significantly.⁹⁸ In Estonia, data from specialised drug treatment centres indicate that opioids (mainly non-pharmaceutical fentanyl or 3-methylfentanyl) were the most commonly reported primary substances for first-time clients entering treatment in 2015. In recent years, fentanyl has become the main injected opioid substance in that country.⁹⁹

Fentanyls are associated with tolerance and withdrawal symptoms. Reports from users suggest the development of tolerance, withdrawal-like symptoms and

physiological dependence similar to those with other opioids.^{100,101} Characteristic withdrawal symptoms include sweating, anxiety, diarrhoea, bone pain, abdominal cramps and shivers or 'goose flesh'.^{40,41}

There is little published information on the management of dependence and withdrawal for fentanyl misuse or its analogues. Methadone has been used. In Estonia, where the most commonly reported primary substances for first-time clients entering treatment in 2015 were fentanyls, most clients received opioid substitution therapy (OST) and methadone in particular.⁹⁹

Other long-term effects

There is some limited evidence that the long-term use of fentanyl has also been associated with:

- hyperalgesia (opioid-induced abnormal pain sensitivity, also called paradoxical hyperalgesia);¹⁰²
- gastrointestinal disturbance;¹⁰³
- immunological dysfunction;¹⁰³
- hormonal disruption;¹⁰³
- muscle rigidity and myoclonus.¹⁰³

Among older people in particular, long-term use of fentanyl is linked to raised risk of fracture and acute myocardial infarction¹⁰⁴ and generally increased mortality.¹⁰⁵

Public health risks: injecting and other high-risk drug-using behaviours

It has been argued that fentanyl and its analogues pose distinct risks for the transmission of blood-borne viruses such as hepatitis C and HIV.⁴⁷ There is also some evidence that use is associated with high-risk behaviours. Users of illicit fentanyl in Toronto, for example, reported engaging in practices that exposed them to blood-borne viruses.⁴⁷ It has also been associated with bacterial infections and vein damage, with one study showing how fentanyl injecting-related harms are exacerbated by the use of lemon juice or vinegar, which can cause vein damage when injected.¹⁰⁰

There have been suggestions that fentanyl-specific harm-reduction information be developed. Commenting on the increase of fentanyl-related deaths in Australia, Alan et al. in 2015 stated that 'An increase in fentanyl-related overdoses and deaths suggests that information about how to reduce harms associated with injecting fentanyl is lacking'. In their study of the non-medical use of fentanyl patches, users reported lack of knowledge of the drug they were using, including exactly what it was, how to extract it and how to measure the dose. Peer networks were identified as the key source of information in drug-using practices, but information shared was poor, even dangerous.¹⁰⁰

Key points

- Fentanyl is a very potent synthetic opioid receptor agonist. When misused, it is associated with a high risk of acute toxicity.
- There are no rapid urine or serum tests for the detection of non-pharmaceutical fentanyls.
- In comparison with heroin, fentanyls have a shorter duration of effect, especially when injected.
- Common features of fentanyl toxicity include: miosis, nausea, vomiting, anxiety, agitation, euphoria, dysphoria, depression, paranoia, hallucinations.
- Fentanyl severe toxicity is characterised by decreased consciousness, apnoea, and respiratory and central nervous system depression. It can lead to deep coma, convulsions and respiratory arrest. Sudden onset chest wall rigidity may be associated with increased risk of mortality.
- In comparison with heroin overdoses, overdoses of fentanyl and analogues are associated with greater risk, and more rapid onset and progression.
- The broad principles of management apply to all opioids, with the following to be taken into account.
- Where the use of fentanyls is suspected, there is a need to call emergency services and transfer to hospital, especially where naloxone is not available in the community, or if there is need for prolonged naloxone administration.
- Guidance is available in the UK on the administration of naloxone in the community and in hospital settings. Overall, the evidence suggests that:
 - A more rapid administration of naloxone is warranted because of the rapid onset of fentanyls.
 - A more rapid escalation of additional doses for naloxone may be needed in comparison with heroin or other opioids.
 - Overall, higher doses of naloxone may be needed for fentanyl patients in comparison with heroin patients.
 - Fentanyl patients may require a longer period of observation in hospital than heroin patients.

Reporting adverse effects of NPS in the UK

- If you do come across a case of suspected harm from any new psychoactive substance (NPS) or other drug, please report it to Report Illicit Drug Reactions (RIDR) at <https://report-illicit-drug-reaction.phe.gov.uk>, a joint initiative between Public Health England (PHE) and the Medicines and Healthcare products Regulatory Agency (MHRA).

- For up-to-date guidance on the management of acute toxicity linked to opioids, including fentanyl, it is recommended that information be sought from the database of the National Poisons Information Service (NPIS), TOXBASE® <https://www.toxbase.org>.
- The NPIS 24-hour telephone helpline (in the UK 0844 892 0111 and Ireland NPIC (01) 809 2566) is available for discussion of more complex cases. When appropriate, senior medical staff can discuss their cases directly with an NPIS consultant clinical toxicologist. Non-UK readers should consult their local or national guidelines and poison information services.

Section 3. Other novel synthetic opioids

In addition to fentanyl and its analogues, in the past five years more than a dozen additional synthetic opioids have entered the illicit opioid market. Some of these novel synthetic opioids have been rediscovered by traffickers from research done between the 1960s and 1990s, when they were described in the scientific literature but never developed into pharmaceutical products.

Newly marketed synthetic opioids have appeared with structures distinct from those used in medical practice. Examples include, but are not limited to, AH-7921 (a benzamide), U-47700 (a compound closely related to AH-7921) and MT-45 (a piperazine):

- AH-7921 is 3,4-dichloro-N-(1-(dimethylamino)cyclohexylmethyl)benzamide;
- U-47700 is trans-3,4-dichloro-N-(2-(dimethylamino)cyclohexyl)-N-methylbenzamide;
- MT-45 is 1-cyclohexyl-4-(1,2-diphenylethyl)piperazine.

These were all first synthesised in the 1970s.⁸ The pharmacology, availability and modes of use of these three substances are outlined in Table 2. The effects desired by users are listed in Table 3.

Unwanted and adverse effects of intoxication

AH-7921, U-47700 and MT-45 have similar profiles of unwanted and adverse effects. Further details are given in Table 4.¹¹⁵

Signs of toxicity¹¹⁵

- Miosis (pinpoint pupils), with the exception of MT-45, which has only a small miotic effect
- Nausea, vomiting
- Anxiety, agitation
- Euphoria, dysphoria
- Depression
- Paranoia
- Hallucinations

Table 2. Pharmacological and other properties of three novel synthetic opioids

AH-7921	U-47700	MT-45
Pharmacology		
<p>AH-7921 is an opioid analgesic that was patented by Allen and Hanburys Ltd in 1976 but that has never been used as or in a pharmaceutical or medicinal product. Thought to be a morphine-like analgesic acting mainly as a μ-opioid receptor agonist. Human data are mostly not available, but animal studies have shown that AH-7921 is approximately as potent as morphine with regard to respiratory depression, antinociception, sedation and miosis (decrease in pupil diameter), Straub tail, decrease in body temperature and inhibition of gut propulsion.^{106,107,108}</p>	<p>U-47700 is an opioid analgesic and is structurally related to AH-7921. Although U-47700 exhibits some κ-opioid receptor agonism, it has far more activity at the μ-opioid receptors.⁴² It is a selective μ-opioid receptor agonist, and in animal models has been demonstrated to have ~7.5 times the potency of morphine.^{109,110} According to user reports, U-47700 acts longer than AH-7921.²⁰</p>	<p>MT-45, also known as IC-6, was developed in the 1970s as an alternative to morphine for analgesia. It is an N,N-di-substituted 4-(1,2-diphenylethyl) piperazine chemically unrelated to other opioid agonists. The pharmacology of MT-45 is complex and involves opioid and non-opioid receptors that have not been fully characterised; however, it has been demonstrated in animal studies to have approximately the same potency as morphine.¹¹¹ It appears that MT-45 has a slow onset of action, greater than 1–2 hours when taken orally, which may increase the risk of toxic overdose from redosing before peak effect is reached.¹¹²</p>
Availability and modes of use		
<p>AH-7921 has been available in Europe since mid-2012 via websites selling 'research chemicals'.^a AH-7921 is sold as a free base and as a hydrochloride salt in a white/off-white powder form,¹⁰⁸ but has also been detected in Japan as a co-ingredient in synthetic cannabinoid and cathinones.¹¹³ AH-7921 is usually consumed orally but can also be used by inhalation/vaporising, nasal insufflation, sublingually, intravenous injection or rectal administration and is sold as a powder, tablet, or capsule.</p>	<p>In the recreational drug market, U-47700 is sometimes referred to as 'pink', because it can be slightly pink in colour. The drug is also known as 'U4'.¹ It is taken orally, nasally, rectally, by smoking, intravenous injection, or by combinations of these routes.²⁰</p>	<p>MT-45 is typically sold on the internet or illicit market as a dihydrochloride salt. Typical routes of administration include oral, insufflation, intravenous and intramuscular. Rectal use has also been reported.⁴⁹ It has been found mixed with other drugs, including synthetic cannabinoids and synthetic cathinones.¹¹⁴</p>

^a It is often sold or discussed on user websites and public media under the alternative name 'doxylam'. This name could be easily confused with that of 'doxylamin' (an antihistamine drug with sedative-hypnotic properties that is present in several over-the-counter medicines); the unintentional use of AH-7921/doxylam bought on the internet for the treatment of allergy or as a hypnotic might have serious health consequences.

Table 3. Desired effects of three novel synthetic opioids

AH-7921	U-47700	MT-45
<p>Much of what we know about its effects comes from reports of people who have used it. Based on this, the effects of AH-7921 appear to resemble those of classic opioids.</p> <p>AH-7921 produces relaxation, euphoria, a physical anaesthetic effect, mental relaxation and pleasant mood lift.¹¹⁵</p> <p>An interesting finding reported by one study was that the users of AH-7921 (as well as of MT-45) report experiences of increased energy.¹¹⁶</p> <p>There are also reports of its use as self-medication to relieve pain or to alleviate withdrawal symptoms due to cessation of the use of other opioids.¹¹⁶</p>	<p>Based on animal models, it is expected that U-47700 produces effects similar to those of other potent opioid agonists, including analgesia, sedation, euphoria.¹¹⁷</p> <p>It has been suggested that U-47700 induces significant euphoria, which is short-lived and causes an urge to keep 'redosing'.¹¹⁸</p>	<p>Effects similar to other opioids.⁴⁹</p>

Signs of severe toxicity

- Severe opioid toxicity produces depression of the respiratory and central nervous systems. If untreated the depression of the level of consciousness can lead to deep coma, convulsions and respiratory arrest.

Management of acute intoxication and overdose

AH-7921, U-47700 and MT-45 require similar management of acute intoxication and overdose. These synthetic opioids are currently not tested as a routine part of most forensic drug screening. However, it has been argued that the clinical approach in managing opioid toxicity and overdose should not change and should include the management of airways and the administration of naloxone to reverse the overdose.¹²¹

As NPS opioids have various potencies, receptor affinities and street concentrations, it has been argued that it is possible only to speculate about the doses of naloxone required for reversal and this should be determined on a case-by-case and drug-by-drug basis.⁴

It has been suggested that emergency responders may have difficulty in identifying MT-45 overdose because the drug produces a small miotic effect (restriction of pupils).¹²¹

Table 4. Unwanted and adverse effects of intoxication of three novel synthetic opioids

AH-7921	U-47700	MT45
<p>A study found that morphine has a twofold greater safety margin than AH-7921, which suggests readier appearance of toxic effects after AH-7921 use.¹¹⁹</p> <p>The side-effects range from milder symptoms (e.g. stomach upsets, light headache) to more severe conditions (e.g. anxiety and panic).¹¹⁶</p> <p>Other reported adverse effects include abdominal pain, constipation, reduced mobility, light-headedness, headache, urinary retention, visual impairment, pain in the mouth.</p> <p>Unwanted adverse effects also include vertigo induced by movement.¹¹⁵</p> <p>Users also reported itching as one of the side-effects of AH-7921 use, as well as other forms of skin irritation. There are also reports of numbing of different parts of the body.¹¹⁶</p> <p>Temperature change, tremors, numbness, blister, seizures, hypertension and tachycardia have also been reported.¹²⁰</p>	<p>Based on animal models, is expected that U-47700 produces effects similar to those of other potent opioid agonists including constipation, itching and respiratory depression.¹¹⁷</p> <p>It has been suggested that U-47700 induces significant euphoria, which is short-lived and causes an urge to keep 'redosing'.¹¹⁸</p>	<p>MT-45 has only a small miotic effect (restriction of pupils or pinned pupils),¹²¹ in contrast to other commonly used opioid drugs.</p> <p>Although MT-45 is structurally unrelated to morphine, it has analgesic and CNS depressant properties similar to those of morphine, including respiratory depression.¹²²</p> <p>Some animal studies suggest a higher toxicity than morphine.¹²²</p> <p>Drug users also report some dissociative-like symptoms.¹¹¹</p> <p>Other reported unwanted effects include nausea, itching, bilateral hearing loss and possible withdrawal symptoms. A unique feature of MT-45 toxicity is its association with ototoxicity – that is, it is linked with hearing loss, with a reported case of bilateral hearing loss lasting for two weeks.^{49,112}</p>
Deaths		
<p>AH-7921 has been associated with fatal overdoses, including a small number of deaths in the UK.^{108,123,124,125,126,127}</p> <p>Deaths associated with AH-7921 seem to occur both at low and high concentrations, possibly a result of different levels of tolerance to the drug.¹²⁸</p> <p>As with other overdose deaths, poly-drug use has been involved in many AH-7921 deaths,^{106,115} but AH-7921 use alone has also been reported.¹²⁸</p>	<p>Deaths reported.^{117,118}</p>	<p>Deaths reported in Europe and elsewhere.^{49,117,129,130,131,132}</p>

Chronic effects and dependence

Despite limited evidence, it is assumed that AH-7921 and U-47700 have a high addictive potential similar to or greater than that of morphine.^{49,133} Reports from users suggest the development of tolerance and of withdrawal-like symptoms with MT-45, AH-7921 and U-47700 is similar to that with other opioids.

Section 4. Concluding remarks and key points

At the time of writing, synthetic opioids, including fentanyls, used for non-medical purposes in the UK can be described as 'low use but high risk/harm' substances. Vigilance is required, as well as improved confidence and competence in the identification, assessment and management of their harms in clinical practice.

The literature suggests that the management of the acute and chronic harms associated with the novel synthetic opioids should be based on the same approach used by clinicians in the management of other acute opioid toxicity and overdose, including airway management and naloxone for the reversal of overdose. The literature also suggests the need for a greater understanding of, and a better response to, the factors specific to these novel synthetic drugs and which make their harms and management different from those for heroin, for example.

Key points

- Synthetic opioids, including novel opioids, are increasingly available on the illicit market and often mis-sold as other drugs.
- The adverse effects of these substances are similar to those of other opioid drugs and include the risk of acute toxicity, overdose and dependence.
- Symptoms of overdose from these synthetic opioids can, however, differ from those of heroin. Fentanyls, for example, appear to cause more rapid respiratory depression.
- As with other opioid drugs, poly-substance misuse (particularly with other sedatives) increases the risk of adverse effects.
- Clinical management of suspected overdoses with synthetic opioids, including fentanyl and analogues, should follow protocols for opioid overdose (airway, breathing and circulation: ABC), with a low threshold for administration of naloxone.

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