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Tackling Synthetic Opioid Misuse: an impending crisis

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Summary:

There is growing concern regarding the increasing prevalence of synthetic opioids and the association between synthetic opioid use, mortality, and a range of health and social harms.

Recognition, assessment and management of synthetic opioids is a key challenge for practitioners working in diverse settings in hospitals, prisons and community services. This paper provides an evidence-based overview of the range and characteristics of synthetic opioids, key risks and prevalence of synthetic opioid-related deaths in England, prevention and management approaches.

Five key areas are critical to addressing the synthetic opioid crisis:

- 1) ensuring improved access to medication suited specifically to addressing synthetic opioid addiction,
- 2) increasing naloxone availability and integrating overdose response with linkage to comprehensive Opioid Use Disorder treatment,
- 3) strengthening prevention efforts targeting the unique risk factors associated with synthetic opioids, including illicit drug markets and emerging trends in drug use,
- 4) optimizing pain management strategies to reduce the need for prescription opioids and minimize the risk of synthetic opioid misuse,
- 5) Raising awareness among healthcare providers, patients, and the general public about the dangers of synthetic opioids, including their potency, addictive nature, and potential for overdose.

Learning Objectives:

After reading this article you will be able to:

1. Describe major types of synthetic opioids, their characteristics and key risk factors associated with their use.
2. Critically discuss assessment and management challenges.
3. Demonstrate knowledge of prevention, assessment and management approaches.

Keywords:

Synthetic opioids, Opioid epidemic, Opioid overdose, Opioid addiction, Opioid-related deaths.

Introduction:

The harm associated with synthetic opioids (SOs) is one of the most pressing public health crises of our time. These substances, including fentanyl and its analogs, are highly potent and have contributed to a dramatic increase in overdose deaths worldwide. Although drug-related deaths and the association with synthetic opioid use is not as pronounced in England as it is in Scotland, Northern Ireland and the USA (van Amsterdam *et al.* 2021), nevertheless, from their analysis of opioid use and related harm in Europe, Pierce *et al.* (2021) conclude that action is needed to stop an emerging crisis in the UK. Their conclusion was shared by Jon Shorrock, programme manager at the Office for Health Improvement and Disparities (OHID), speaking at a conference in April 2024: *‘Drug poisoning and drug misuse deaths are at record highs in England having almost doubled since 2012. These deaths predominantly involve opioids and now increasingly synthetic opioids’* (Shorrock 2024).

The extent to which SOs contribute to drug-related deaths in England is not entirely clear, and delays in testing and recording systems mean that the impact of SOs is probably undercounted (Gov.UK 2024). However, the risks posed by SOs extend beyond overdose, impacting communities, healthcare systems, and law enforcement. Understanding the scope of the harm they cause is essential for crafting effective policy, prevention, and treatment solutions to mitigate their effects on individuals and on society as a whole. Recognition, assessment and management of SOs is a key challenge for practitioners who also have an important role in developing and implementing effective interventions.

This article details the types and characteristics of SOs, the modes of use, their effects, prevalence, and the role they play in drug-related deaths. It then considers the challenges and barriers to assessment and to delivering an effective policy and practice response.

Synthetic opioids and their characteristics

There are four main types of SOs, Nitazenes, Fentanyl analogues, U-type compounds & Buprenorphine-like opioids. They can be divided into 2 categories, pharmaceutical fentanyls (such as fentanyl, sufentanil, remifentanil, and alfentanil) and non-pharmaceutical fentanyls (NPF) which are fentanyl analogues or designer fentanyls (such as ocfentanil, butyrfentanyl).

SOs are used legally in medical care. The fentanyl analogues currently licensed as medicines for human use in the UK are fentanyl, alfentanil, remifentanil and sufentanil. These are used to

relieve pain but also have euphorogenic effects and have the potential for misuse. Pharmaceutical fentanyl is used in hospital practice, especially in intensive care units and operating theatres, for anaesthesia and post-operative pain management. In terms of therapeutic potency compared with morphine, fentanyl is 50-100 times more potent, alfentanil 30 times and sufentanil 500 times more potent (ACMD 2020).

These prescribed substances can be diverted into street use and SOs are also synthesized in illegal laboratories. SOs act on the same targets in the brain as natural opioids e.g. morphine. Illicit fentanyl analogues such as carfentanil are 10,000 times more potent than morphine in analgesic properties. Because these substances are cheap to produce and are extremely potent, illicit suppliers find it lucrative to replace or supplement opiates such as heroin with these. They are also easy to transport in small quantities which can then be distributed locally, for instance in prisons, or internationally. Substantial profits can be made by local distributors who may dilute the substances further using unknown materials (ACMD 2020; Shafi *et al.* 2022).

As noted by Karila *et al* (2019), since 2010, new SOs, structurally different from fentanyl, have emerged on the market. Among them are AH-7921 (benzamide analog), MT-45 (piperazine analog), or U-47,000 (an isomer of AH-7921 and 7.5 times more potent than morphine).

The most common group of nitazenes in the UK are 2-Benzyl benzimidazole, originally developed in the 1950s as analgesics, but not approved as human or veterinary medicines because they were found to be so potent. Brorphine-like opioids are less common in this country than some of the other opioids, but still of possible concern (ACMD 2022). Nitazenes and brorphine-like opioids are of particular interest because they pose significant risks of overdose and because there is limited understanding of their pharmacological effects. Although nitazenes, and brorphine-like compounds are structurally distinct from traditional opioids, they interact with the same opioid receptors in the brain, leading to effects that can be far stronger than morphine or fentanyl (ACMD 2022). In this group the strength of Protonitazene is 1.07-1.29x greater than fentanyl and 130 x greater than morphine and Isotonitazene roughly equal in strength to fentanyl and 2.5x greater than morphine (Edinoff *et al.* 2023).

Clandestinely produced SOs have been encountered in powder form and have been identified on bottle caps and spoons, which demonstrates their abuse as replacements for heroin or other opioids. These drugs are also encountered as tablets, sold as benzodiazepines or pain relief medication in blister packs or boxes that look like legitimate pharmaceutical products (EUDA

2024a; US Department of Justice 2017).

The increasing presence of SOs in the illicit drug market has raised concerns as users may be unaware of the drug's strength and its ability to cause respiratory depression at even low doses. Furthermore, the clandestine production of these substances makes it challenging for regulatory bodies and healthcare providers to monitor their distribution and mitigate public health risks effectively. Synthetic opioids, particularly nitazenes, some of which are 500 times stronger than morphine, have been detected in at least 20 postcodes in the UK since September 2023 (OHID 2024).

Mode of use

SOs are produced in several forms, including powders, tablets (such as standard pills or lozenges), skin patches (transdermal patches), and liquids. They can be taken into the body in many ways: by swallowing, snorting through the nose, smoking, injecting, applying to the skin, or placing under the tongue, in the vagina, or in the rectum. They can also be inhaled by vaping. When a transdermal patch is chewed before being swallowed, the body may absorb more of the drug than it would from swallowing alone. Even after a patch has been worn for treatment, it often still contains a significant amount of the drug. Because of this, people may try to extract the remaining drug from used patches to take it in other ways, such as by injection or snorting.

Drug effects

Synthetic opioids effect individuals differently depending on size, body weight and general health. Other factors include amount and strength taken, administration route, degree of tolerance, whether other psychoactive drugs have been taken at the same time. These factors all result in different duration of onset of symptoms and effects. Short term effects include euphoria, relaxation, pain relief, nausea, vomiting, fever, sweating, hypotension, slow breathing and heart rate.

As reviewed by Shafi *et al.* (2022) and Salle *et al.* (2019), synthetic opioids effect all the major body systems.

Table 1: SO effects on body systems

Neurological	- Most common: reduced consciousness (drowsiness, disorientation, lethargy, coma resulting in death)
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	- Miosis (small pupils) - Hyperalgesia (increased pain), anesthesia (loss of sensation) - Dizziness, depression, dissociation, memory loss - Poor psychomotor skills, sleep disturbance - Fentanyl overdose: body stiffening, seizures, delayed brain damage - Cerebral hemorrhage (after acetylfentanyl intoxication) - MT-45: tingling, weak hands, balance problems, ear toxicity - U-49900: loss of taste, smell, touch
Respiratory	-Most dangerous: respiratory depression (slowed/blocked breathing) - Cough suppression - Hypoxia (low oxygen), -Cyanosis (blue skin) - Pulmonary edema (fluid in lungs), Pulmonary congestion - Fentanyl/analogs: chest wall rigidity, apnea (stopped breathing), even at low doses
Cardiovascular	-Acute cardiac effects: hypotension, bradycardia, shock/ chest pain - Acetyl fentanyl & 4-methoxybutyrfentanyl: increased heart rate - Chronic use: enlarged heart, fibrosis (scarring), arteriosclerosis (hardened arteries)
Gastrointestinal & Urinary	- Constipation, bowel dysfunction - Less digestive secretions, reduced absorption - Esophageal dysmotility, gastric hytomobility (slow stomach movement), paralytic ileus - Cramping, nausea, vomiting, anorexia, weight loss - Urinary urgency or retention - Liver effects: MT-45 → increased liver enzymes - Hepato-pancreatic: biliary colic, epigastric pain

Other effects:

- Long term use effects the endocrine system by inhibiting the hypothalamic-pituitary gonadal axis resulting in a decrease in testosterone and estradiol release. This can manifest clinically as loss of libido and impotence in males, amenorrhea and infertility in females. All these symptoms may also lead to reduced energy levels and depression. (Kotlińska-Lemieszek and Żylicz 2022)
- Opioids can also inhibit the hypothalamic-pituitary-adrenal axis, which sometimes can present clinically as an adrenal crisis.
- The androgen deficiency promotes osteoporosis. In chronic use, insulin resistance can appear.

- Opioid use can lead to immunosuppression increasing risk of infections and stimulating gastrointestinal and pulmonary cancer.
- Decreased bone density and increased risk of fractures are well recognised in long term opioid use (Kotlińska-Lemieszek and Żylicz 2022).
- Opioid use can impair sleep quality and pattern leading to daytime sleepiness and fatigue.
- Opioids can also trigger or exacerbate sleep apnoea in predisposed individuals. Kotlińska-Lemieszek and Żylicz 2022).

Key risk factors for SO-related deaths

Reviews and studies have identified a number of risk factors and risk contexts associated with the use of SOs and the involvement of SOs in deaths. For example, data from the USA and Europe show that males, compared to females, tend to have greater drug overdose mortality and that there is an increase in deaths from SOs (Butelman *et al.* 2023; EUDA 2024a; EUDA 2024b). In the UK in 2023, among males, there were 127.6 drug-poisoning deaths registered per million population (3,645 deaths), compared with 59.8 deaths per million among females (1,803 deaths) (OHID 2024). Although late adolescence and young adulthood are periods of increased risk, the rise of older adults, aged 55 and older, seeking first-time treatment (EUDA 2024a) may indicate an increased risk of death occurring. Socio-economic factors and marginalization of some population groups, such as homeless people, have been identified as particularly at risk (Scheibein *et al.* 2020; Devany 2019); contexts such as prisons are noted as ‘risk environments’, with particular relevance to deaths from SO use (Duke *et al.* 2023). People who have a history of problematic drug use and polydrug use are also at greater risk of drug-related mortality (Armoon *et al.* 2021).

Prevalence of SO-related deaths

The European Drug Agency (EUDA 2024a) estimated around 6,400 drug-induced deaths in 2022 with considerable variation between European countries. This represents a mortality rate of 22.5 deaths per million population aged 15 to 64, due to overdoses in 2022. The report notes that there is growing concern over deaths linked to SOs but, with a few exceptions, these drugs are not routinely monitored or reported at EU level. It is likely, therefore, that deaths linked to SOs are under-reported.

The UK has one of the highest rates of drug-related deaths in Europe. Global markets are

rapidly evolving, reflecting growing alarm that the UK may potentially face a similar ‘opioid epidemic’ as in the USA. Data from the most recent figures published by the Office of National Statistics reveal drug-related deaths in England and Wales were 5,448 in 2023 (ONS 2024).

The UK’s first nitazene death was recorded in 2019 and a big influx in the summer of 2024 has seen nitazenes detected all over the country. The Office for Health Improvement and Disparities (OHID) and the National Crime Agency (NCA) confirmed that there were 179 deaths involving one or more nitazenes occurring between 1 June 2023 and 31 May 2024 in England (GOV.UK 2024a). Over this period, nitazenes were present in all deaths involving illicit fentanyl, or analogues of fentanyl. However, from available information, it is not always possible to determine whether fentanyl involved in a death was illicit or pharmaceutical.

Table 2 shows the number of deaths associated with different nitazene compounds identified by laboratory tests. In 17 cases out of the total 179 deaths, there was no confirmation of the specific compounds involved.

Table 2. Deaths associated with Nitazene use

Nitazene detected	Deaths
Protonitazene	73
N-desethyl isotonitazene	46
Metonitazene	34
N-pyrrolidino protonitazene	16
Isotonitazene/ Etonitazene	2/2
N-pyrrolidino etonitazene/ N-desethyl etonitazene/ Metodesnitazene	1/1/1
Unspecified nitazene	17

Source GOV.UK 2024

Note: more than one nitazene was detected in some deaths, so the sum of detections is greater than the total nitazene deaths.

Deaths involving nitazenes (n=179) have been recorded in every region of England with notable differences across the regions. For example, between June 2023 and May 2024, the region with the highest rate was the East of England, with 33 deaths, followed by the East Midlands with 29 deaths. Only 3 deaths were recorded in the North East, with a range of 12 to 25 deaths occurring in the remaining six regions (GOV.UK 2024). Examination of the reasons for regional differences is lacking in the available research. Analyses of differences in drug-related deaths between England and Scotland, and between Europe, the USA and the UK, suggest that a complex range of factors is at play, including drug availability, an ageing cohort, the number of people not in drug treatment and the nature of available treatment services in an area (Amsterdam *et al.* 2021; Pierce *et al.* 2021).

Synthetic opioids: a looming crisis?

The rise of SOs in Europe, particularly those linked to fatal overdoses and acute poisonings, has alarmed health services and law enforcement agencies.

Some potential reasons why synthetic opioid use has become so pervasive have been postulated to include lower production costs, stronger or longer lasting highs, and increasingly efficient synthesis by manufacturers (Ciccarone 2021; Kline *et al.* 2021).

These substances are easily transported and hidden, and they can be produced in small quantities to yield large numbers of street-level doses. While Europe's opioid crisis is not as severe as the US fentanyl crisis, it is still a significant public health concern. (EUDA 2024b)

The European Union Agency for Criminal Justice Cooperation (Europol) has identified 49 SOs in the European drug market since 2009, with 34 being fentanyl derivatives. In 2018, six new opioid derivatives emerged. SOs are now the fourth most commonly monitored substance group in Europe, following synthetic cannabinoids, cathinones, and phenethylamines. Fentanyl derivatives accounted for over 70% of SO seizures in Europe in 2017. (EUDA 2024b).

The harms associated with opioid use and the importance of addressing unmet needs in opiate dependence to avoid overdose have been well documented in the literature (Herlinger and Lingford-Hughes 2021).

Synthetic opioid exposure has been demonstrated to confer nearly twice the risk of fatal overdose relative to prescription opioids or heroin (Florence *et al.*, 2017; Manchikanti *et al.*,

2022). The combination of minimal production costs and extraordinary potency renders fentanyl particularly suitable for admixture with heroin and other illicit substances (Volkow & Blanco, 2021). In addition, fentanyl and related analogues are frequently encountered in counterfeit formulations designed to mimic the appearance of widely prescribed opioids and benzodiazepines, colloquially termed “pressed pills” (Armenian et al., 2018).

According to the U.S. Drug Enforcement Administration (2021), synthetic opioid-related deaths are frequently attributable to their use as low-cost adulterants, though intentional consumption also occurs. The inadvertent exposure of users to fentanyl and its analogues, now routinely detected in cocaine, methamphetamine, heroin, and falsified pharmaceuticals, is regarded as a principal driver of mortality (Han et al., 2019).

The heightened overdose risk associated with synthetic opioids compared to heroin stems from their far greater potency and availability within the drug supply (Skolnick 2022). A dose that might be “normal” for heroin can become fatal if replaced with fentanyl or carfentanil without immediate medical intervention. In addition, while a heroin overdose may take 20–30 minutes to become deadly, fentanyl can cause severe, life-threatening respiratory arrest within just 2–5 minutes (Skolnick 2022).

In addition, fentanyl derivatives also have significant risk of addiction and could have adverse effects on health and social problems commonly associated with opioid use. Fentanyl analogs are a major cause of poisonings, fatal or not, in the United States and in Northern Europe. In other countries, their presence is less visible.

In the following sections, we consider prevention approaches which address the wider public health aspects of the use of opioids and synthetic opioids before discussing what can be done in treatment settings to identify, assess and manage synthetic opioid use and related harms.

Prevention

Prevention is a key aspect of managing the problems of mortality, morbidity and associated social sequelae with SOs and associated drug use. The importance of prevention and early intervention has been stressed in policy documents and in the research (e.g. Black 2021; Volkov *et al.* 2019). For this purpose, **universal and targeted prevention strategies** are crucial to curb prescription opioid misuse and synthetic opioid threats. Main prevention

approaches are summarized in Box 1.

Box 1: Key prevention approaches

Education and training for healthcare professionals, especially for psychiatrists working in community settings, A&E, prisons and primary care on identification of those at high risk, harm reduction, principles of opioid substitute prescribing and safer pain management practices is essential.

Monitoring opioids prescription data in primary and secondary care helps identify potential misuse and inform interventions.

Naloxone should be readily available for overdose reversal in all relevant settings, e.g. targeting those who are homeless, recently released from prison.

Community-based interventions can prevent substance use disorders in at-risk populations by focusing on hard-to-reach populations, developing integrated care with third sector agencies, and planning for more rapid interventions including opiate substitute treatment (OST). It is important to bear in mind that in addition to OST simultaneous delivery of psychosocial interventions is recommended as improving outcomes.

A broad **community-based intervention strategy at national and local level should consist of** implementing evidence-based programs in schools, families, and communities to prevent substance use disorders. Raising public awareness about the dangers of prescription drug and synthetic opioid misuse is another important aspect in this context.

Between June 2023 and May 2024, most deaths were reported to the National Crime Agency (NCA) or the Office for Health Improvement and Disparities (OHID) through local networks. Work is ongoing to reduce the health risks linked to rising use of these and other drugs. As part of this effort, OHID is working with other government groups, including the Synthetic Opioids Taskforce, to improve drug monitoring and create an early warning system. Since April 2024, laboratories have been sharing toxicology results from fatal overdose cases when coroners allow the data to be used. This information is added to the joint NCA and OHID log of tracked cases (GOV.UK, 2024a).

The role of opiate substitution treatment (OST) in the management of heroin dependence is

well recognised as are its benefits. In the UK recently three main changes have meant that an update was necessary in the existing national guidelines (Gov.UK 2023; Gov.UK 2024a)

- our knowledge base (research evidence, data and clinical experience) has grown, and so has the availability of different buprenorphine formulations
- we have more evidence that engagement with OST is associated with reduced mortality across a range of conditions
- the arrival of potent illicit synthetic opioids in the UK has reinforced the importance of engaging and retaining greater numbers of opioid dependent people in treatment.

Recent data indicate that in UK 70% of patients are prescribed Methadone and 30% Buprenorphine in addiction treatment services. NDTMS data indicate that in UK in 2023 709 drug related deaths were associated with Methadone and 46 with Buprenorphine. Overall, in the past decade, Methadone is associated with ten times more deaths each year compared to Buprenorphine. The new guidance recommends increased use of Buprenorphine due to less risk of respiratory depression, shorter time duration required to achieve optimal dose, and lower risk of diversion. The possibility for rapid prescribing, for these reasons, is more with Buprenorphine, including on first day of attendance, as well as ability for take away doses to be prescribed much earlier and for less duration. There is a need to change current treatment protocols to implement these recommendations and widen the net in provision of OST to underserved populations such as the homeless and those engaging poorly with services. The use of long acting depot injection of Buprenorphine (Buvidal) adds another tool to the clinician's armamentarium (Gov.UK 2024a).

Identification/Assessment

In specialized addiction services, Nitazene strip tests are used for patients who use opioids and are at high risk. The Rapid Response Test Strips are a rapid visual immunoassay for the detection of adulterants in substances before they are used. These strips are given to service users who are educated how to test their personal illicit drug supply for presence of Nitazenes and required to inform relevant staff of results. If positive, the advice should be given to immediately discard the drugs and not use any of this batch. Harm reduction advice should be given at point of issuing the test strips. These are not a urine drug screening test. The test does not take longer than five minutes including preparation. A positive result can be interpreted typically by 60 seconds. It is recommended not to read results after 10 minutes. A positive

result indicates the presence of nitazene only and does not indicate quantity. A negative result does not at any time rule out the presence of nitazene as it may be present below the minimum detection level of the kit. There is a possibility that technical or procedural errors as well as other substances and factors may interfere with the Rapid Response Nitazene Test Strip (Liquid/Powder) and cause false results. At present there is no other way to identify the presence of Nitazines.

Information from some of the manufacturers and suppliers makes clear the limitations of test strips. For example, it makes clear that they:

- will not detect drug concentrations below specified limits or may fail to detect a drug that is present (sometimes called a false negative)
- may not detect all variations of a drug type
- may not be used correctly
- may fail because the drug does not dissolve properly, or other substances interfere with the test
- do not indicate the presence of potentially harmful drugs other than those being tested for
- do not indicate the quantity of a detected drug.

Their results can also be difficult to read, especially in low light.

Test strips therefore cannot indicate whether the sample tested would or would not cause harm or possible overdose (OHID 2024a).

Box 2: Key messages to patients who are using Nitazine test strips and deemed at high risk

- | |
|---|
| <ul style="list-style-type: none">• Mixing different drugs is more likely to cause an overdose especially using concurrently benzodiazepines or drinking alcohol. Try to use one at a time. If you are going to mix drugs, use less of each.• Try not to use drugs alone, and prevent your friends from using alone. Be alert to signs of overdose in your friends. The signs include difficulty breathing, blue colouring to the lips or fingertips, unresponsiveness, and limp limbs.• When using with friends, use at intervals of at least a few hours. Wait for the peak effects to pass before the next person uses.• Always carry naloxone. It's available from all treatment providers. If someone overdoses, give naloxone to them and call an ambulance immediately. |
|---|

- Naloxone only works on opioids. If you suspect someone has overdosed give them naloxone even if you're not sure they have taken an opioid. It will not harm your friend.
- If you use opioids every day your local drug treatment service can support you and prescribe alternatives such as methadone and buprenorphine. Even if abstinence isn't your goal these alternatives can help keep you safe. You will know what you are taking and your risk of overdose may be reduced.
- If you are already in treatment for opioid dependence and you don't want to use on top, speak to your worker and make sure you're getting the right dose of Methadone or Buprenorphine.
- Use WEDINOS Sample Testing to test your drugs if you can spare a bit; but it takes time to get the results back so go easy in the meantime.

Source: Change Grow Live 2025 and multiple sources compiled by the authors.

Management of an overdose

Risk factors for opioid overdose are listed below in Box 3. Many risk factors for opioid overdose generally apply to synthetic opioid overdoses as well. However, some factors may be more pronounced with synthetic opioids due to their potency and unpredictable nature.

Box 3: Risk factors for opioid overdose

Risks are higher if the individual -

- Has an opioid use disorder.
- Injects opioids.
- Starts using opioids again after a break (for example, after detoxification, being in jail, or stopping treatment).
- Uses prescription opioids without medical input.
- Takes a high daily dose of opioids (more than the equivalent of 100 mg of morphine).
- Mixes opioids with alcohol or other drugs that slow down breathing, like sleeping pills, anxiety medications (such as benzodiazepines), barbiturates, some anaesthetics, or certain painkillers.
- Has other health problems, such as HIV, liver or lung disease, or mental health issues.
- Is male, older, or in a low socio-economic group — these groups are more likely to overdose compared to women, younger people, or those with higher socio-economic status.

Source: World Health Organization (2023) – Opioid Overdose

Box 4: Risk Factors Specific to Synthetic Opioids:

- **Unpredictable Potency:** Synthetic opioids like fentanyl and its analogs can vary significantly in potency, making it difficult for users to accurately judge their dosage. This unpredictable nature increases the risk of accidental overdose.
- **Adulteration:** Synthetic opioids are often illicitly manufactured and may be mixed with other substances, including other drugs, fillers, and cutting agents, further increasing the risk of unpredictable and potentially fatal reactions.
- **Lack of Awareness:** Many users may be unaware that their drug supply contains synthetic opioids, making it difficult to take appropriate precautions (Edinoff *et al.* 2023).
- **Due to varying potencies, half-lives and uncertain amount of synthetic opioids in the illegal drug, the onset of OD can be very sudden.**

Use of Naloxone is a main approach in the management of an overdose. Box 4 (adapted from Salle *et al.*, 2019, p305) provides information and advice on the use of Naloxone, which is a main approach to management of an opioid overdose.

Box 5: Management of opioid overdose

- Opioid overdose affects the brainstem and cortical centres regulating breathing, and can lead to respiratory depression and death.
- Initial management should prioritize protecting the airway, maintaining breathing and circulation.
- Naloxone is a competitive mu-opioid receptor antagonist that rapidly reverses opioid effects.
- Administration routes include intravenous (IV), intramuscular (IM), intranasal, intraosseous, subcutaneous, endotracheal, inhalational, and sublingual.
- Intravenous administration is preferred as it allows dose titration to the desired effect while minimizing acute withdrawal risks.
- In community settings or where IV access isn't possible, intramuscular injection is a good alternative, though it carries a higher risk of unpredictable absorption of the Naloxone and acute withdrawal.
- Intra-nasal naloxone is gaining popularity in communities to avoid needle-stick injuries.

- Synthetic opioids (which are highly potent, fast-acting, and long-lasting) make reversal more difficult.
- Management of synthetic opioid overdoses often requires larger or more frequent naloxone doses than typically recommended and longer periods of observation.

Challenges and barriers

SOs like other novel psychoactive substance groups constantly evolve. Therefore, surveillance and monitoring programs are critical to keep up with the associated public health challenges. The Office for Health Improvement and Disparities (OHID) in the Department of Health and Social Care has been working with the National Crime Agency (NCA) to monitor deaths associated with illicit use of potent synthetic opioids in the UK (GOV.UK, 2024)

The information they provide is necessary to prioritize SOs for international review and eventual scheduling and regulation. It is imperative to implement regional drug testing and forensic services where they do not exist. In addition, laboratories must modify their current methodologies or develop new forensic and toxicological analytic methods to detect emerging drugs. This can be challenging as data about SOs emergence differ between regions and become rapidly outdated. (GOV.UK, 2024)

Drug testing should be more regularly carried out in primary and secondary care settings as well as in the criminal justice system.

The global spread of synthetic opioids (SOs) is a serious issue that requires coordinated international responses. These substances are widely accessible on the dark web, easy to hide, and can be delivered through standard or express mail services. Clinicians should be aware that commonly used detection kits may not identify fentanyl analogs or newer synthetic opioids, and they must remain vigilant for signs of opioid use, such as slow or shallow breathing, bluish skin (cyanosis), and pinpoint pupils (miosis). In such cases, Naloxone remains the first-line treatment for opioid intoxication. Naloxone is widely recognized as an effective intervention for reversing opioid-induced respiratory depression and has saved countless lives (Albores-García et al., 2023).

Because fentanyl and other synthetic opioids are extremely potent, multiple doses of Naloxone—or repeated administrations of the nasal spray Narcan® where available—may be required, along with extended monitoring periods. Naloxone works by binding to opioid receptors without activating them, thereby displacing opioid drugs and reversing the life-threatening respiratory depression caused by heroin, fentanyl, and other synthetic opioids (Albores-García et al., 2023).

Another challenge within Addiction Specialist treatment services is to adopt proactive outreach approaches targeting high risk populations and thus expand the cohort being treated with OST. The current widespread local clinical guidance on prescribing of OST needs to be updated with increased use of Buprenorphine and associated practices mentioned earlier.

Treatment challenges are also present in the awareness of risks on prescribing of pain management medication by doctors especially in chronic pain which can lead to iatrogenic addiction to opiates. Training and education at primary and secondary is required to address this.

Application and integration of ongoing research and evidence-based treatment, as well as protocols and the integration and collaboration of addiction consultants with other specialities and GPs for inpatient clinicians may also overcome the preceding challenges Morris (2022))

What do we need to do? How to improve?

Although it is not within the scope of this paper, more attention is needed to pain management and OUD. Understanding pain is important to further understand the neurobiology of these disorders and to help develop more effective prevention and treatment interventions. In the meantime, 5 areas are central to reversing the opioid crisis: (1) improving treatments for chronic pain and improved opioid prescription practices, (2) expanding access to medications for OUD, (3) expanding the availability of naloxone and developing models to link patients who experience overdose to OUD treatment, and (4) improving prevention focused on the risk factors for opioid misuse and OUD, (5) Raising awareness among healthcare providers, patients, and the general public about the dangers of synthetic opioids, including their potency, addictive nature, and potential for overdose.

Achieving these goals requires reversing the stigma attached to medications for OUD,

removing infrastructural barriers to their adoption, and expanding the engagement of healthcare professionals, including psychiatrists and those in criminal justice settings, in OUD treatment. Against this background strategies to address the psychosocial factors that lead people to use opioids and other drugs are necessary.

Overdose prevention centres where people can use their own drugs in a monitored and safe space with professionals on hand to intervene in the event of an overdose is an avenue which needs implementation in the UK. These were first set up in Switzerland more than 20 years ago and the evidence base for them if resourced properly is substantial. This also provides an invaluable opportunity to provide additional support to the most marginalised people, who can be offered referrals to relevant social, health and drug treatment services. The Faculty of Public Health has led calls from more than 100 public health, medical, academic, drug treatment and advocacy organisations calling for overdose prevention centres in the UK. The first such centre opened in Glasgow on the 13th of January 2025 with support from the Scottish Government.

Drug checking services, where the public can submit substances for testing to find out what's in them- giving healthcare professionals and drug workers an opportunity to offer advice and referrals to other support if needed. If people had access to these services, they could check if their substances contain nitazenes or other dangerous drugs and avoid inadvertently consuming them.

Challenge stigma, faced by people who use drugs. Stigma forms a key barrier stopping people from engaging with services that would otherwise help them keep themselves safe. People with the most harmful patterns of drug use often experience other problems including socioeconomic deprivation, homelessness, and trauma, which have led to or exacerbated harmful relationships with drugs. Stigma only makes their lives harder and may aggravate the factors which led them to develop problems with drugs in the first place (Volkow et al. 2019).

Conclusions/ Implications

SOs and its analogues pose a significant and evolving threat to public health. Their high potency and unpredictable nature increase the risk of overdose and death.

Users are often unaware of the presence of these potent substances in their drugs. This highlights the need for increased harm reduction strategies and public health messaging.

Higher doses of Naloxone may be required to reverse overdoses involving synthetic opioids.

A focus on prevention is crucial. Waiting for overdoses to occur and relying solely on naloxone is insufficient.

Recommendations for Practicing Psychiatrists

This overview of the increasing challenges posed by a rise in the availability and use of SOs, indicates the following recommendations.

Educate patients: Discuss the risks associated with illicit drug use, including the potential presence of fentanyl and other synthetic opioids.

Assess for risk: Screen patients for opioid use disorder and assess their risk of overdose.

Adopt harm reduction strategies:

- Discuss safer use practices, such as avoiding mixing opioids with other substances and not using alone.
- Provide information on naloxone and encourage patients to carry it.
- Connect patients with harm reduction services, such as needle exchange programs and overdose prevention training.
- Offer support for substance use treatment, including opiate substitute treatment and encourage wider use of Buprenorphine with rapid prescribing practices.

Advocate for policy changes: Support policies that address the opioid crisis, such as increased access to treatment, harm reduction programs, and overdose prevention initiatives (Lovrecic et al., 2019).

Author contribution:

Karim Dar originally conceptualised the article, undertook literature searches and led on the writing of the paper (review, editing and supervision). Nadine Ahmed undertook literature searches and contributed to writing of the paper under supervision. Betsy Thom contributed with writing (review & editing) the paper.

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MCQs

1. Synthetic Opioids:

- a) are significantly more potent than morphine
- b) a major cause of drug related deaths
- c) are sold in blister packs similar to legitimate medication
- d) depress the respiratory system
- e) all of the above (T)

2. Synthetic drug use can be detected in routine clinical practice by:

- a) Urine drug screening
- b) Oral saliva Testing
- c) hair sample testing
- d) Nitazine strip tests on patient drug sample (T)
- e) Blood tests

3) The key factors in recognition of synthetic opioid use include:

- a) awareness in health care professionals and educating patients (T)
- b) history of respiratory disease
- c) history of alcohol dependence
- d) history of seizures
- e) history of hypertension

4) In the prevention of synthetic opioid related overdoses and deaths key interventions are:

- a) raising awareness in high risk populations
- b) provision of Naloxone to high risk patients in higher doses
- c) harm reduction advice to patients especially not using drugs alone
- d) Therapeutic dosages of Methadone or Buprenorphine
- e) all of the above (T)

5) The key challenge to improve provision of care for this patient group are:

- a) stigma associated with drug use disorders (T)
- b) poor motivation by patients

- c) lack of resources
- d) a focus on harm reduction measures
- e) ineffectiveness of opioid substitution treatment

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