Review

Synthetic opioids: a review and clinical update

Abu Shafi, Alex J. Berry, Harry Sumnall, David M. Wood and Derek K. Tracy

Abstract: The term 'opioids' refers to both the natural compounds ('opiates') which are extracted from the opium poppy plant (*Papaver somniferum*) and their semi-synthetic and synthetic derivatives. They all possess relatively similar biochemical profiles and interact with the opioid receptors within the human body to produce a wide range of physiological effects. They have historically been used for medicinal purposes, their analgesic and sedative effects, and in the management of chronic and severe pain. They have also been used for non-medicinal and recreational purposes to produce feelings of relaxation, euphoria and well-being. Over the last decade, the emergence of an illegal market in new synthetic opioids has become a major global public health issue, associated with a substantial increase in unintentional overdoses and drug-related deaths. Synthetic opioids include fentanyl, its analogues and emerging non-fentanyl opioids. Their popularity relates to changes in criminal markets, pricing, potency, availability compared to classic opioids, ease of transport and use, rapid effect and lack of detection by conventional testing technologies. This article expands on our previous review on new psychoactive substances. We now provide a more in-depth review on synthetic opioids and explore the current challenges faced by people who use drugs, healthcare professionals, and global public health systems.

Keywords: fentanils, fentanyl, laboratory testing, new psychoactive substances, NPS, opioid crisis, overdose, public health, synthetic opioids

Received: 16 August 2021; revised manuscript accepted: 31 October 2022.

Introduction

New synthetic opioids are a major public health concern. This narrative review expands on the authors' 2020 publication on new psychoactive substances (NPS),[1] and we now provide a more in-depth review on synthetic opioids, including their historical emergence, mechanism of action, mode of use, acute harms, chemical structures, management of acute toxicity and overdoses, dependence and withdrawal syndromes and current challenges faced in laboratory testing. Inevitably, in a single paper such as this, there are limitations to the amount of information that can be provided about individual compounds and their global impact. However, the included relevant representative literature referenced in this paper can provide further reading on the topic.

Historical emergence

Historical records regarding the analgesic use of the opium poppy plant (*Papaver somniferum*) date back to 3400 BC in Mesopotamia, when the ancient Sumerians extracted opium from the milky sap of the plant and referred to the bright red flowers as 'the joy plant'.[2–4] However, it was not until the nineteenth century that the plant's natural alkaloids and active ingredients started to be systematically isolated and analysed, leading to the discovery of morphine (1805), codeine (1832) and thebaine (1835).[5–7] This was followed by the development of more potent and efficacious semi-synthetic opioid medications (synthesised in the laboratory from naturally occurring opium compounds), which included diamorphine (heroin) (1874), oxymorphone (1914), oxycodone (1916) and hydrocodone (1920).[8–13] Although first developed as an antitussive, the euphoric and well-being effects associated with heroin soon became sought after for non-medical purposes, leading to concerns from the early 20th century about dependence.[14,15]

Correspondence to:
Derek K. Tracy
West London NHS Trust,
Trust Headquarters, 1
Armstrong Way, Southall
UB2 4SD, UK.
**derek.tracy@westlondon.
nhs.uk**

Abu Shafi
South West London and
Saint George's Mental
Health NHS Trust, London,
UK

Alex J. Berry
Division of Psychiatry,
University College London,
London, UK

Harry Sumnall
Liverpool John Moores
University, Liverpool, UK

David M. Wood
Clinical Toxicology, Guy's
and St Thomas' NHS
Foundation Trust, London,
UK; Clinical Toxicology,
Faculty of Life Sciences
and Medicine, King's
College London, London,
UK

Legislation to address controlled use

Following the introduction of the Hague Opium Convention in 1912, which obliged signatories to limit the manufacture, sale and use of heroin and morphine to primarily medical and scientific uses, international legislation moved towards stricter controls. The Geneva Convention of 1925 placed further controls on the production and international trade of heroin[16–18] and alongside the introduction of the Limitation Convention in 1931, a significant decrease was observed in manufacture and consumption.[19,20] The Single Convention on Narcotic Drugs (1961; and subsequent conventions in 1971 and 1988) placed opioids (and precursors) including heroin, methadone, morphine, and opium into Schedule 1, representing 'substances with addictive properties, presenting a serious risk of abuse' and subject to the strict international controls. Despite these international controls, clandestine organisations responded to the profitability of the then controlled opioids, leading to the development of an illicit international market in drugs.[21–23]

Creation of synthetic opioids

Pharmaceutical companies continued with the development of synthetic opioids, defined as 'synthesised in the laboratory without the use of naturally occurring opium compounds', throughout the 20th century for human and veterinary medicine, leading to the discovery of meperidine[24] in 1939 (with a different chemical structure to morphine but with similar pharmacological properties), followed in 1946 by the synthesis of methadone.[25] In 1959, fentanyl was developed and became a leading analgesic and anaesthetic agent due to its higher potency relative to morphine (50–100 times greater) and heroin (25 times greater), quicker absorption, and shorter time for onset of effects.[26–29] However, these properties also made it attractive for non-medical use, and fentanyl and its analogues soon appeared on the controlled market and were thereafter controlled under the UN Single Convention in 1961 (under Schedule I, and for those with no medical utility, Schedule IV).[30] More recently, over the last decade, new synthetic opioids (e.g. carfentanil and ocfentanil), including non-pharmaceutical products, have been implicated in an international opioid crisis and the associated increase in unintentional overdoses, poisonings, and drug-related deaths.[31–35] The growing number of synthetic opioids on the controlled drug market, the ability for potent products to be easily transported in relatively small amounts (such as *via* the postal service) and their associated morbidity and mortality, means that they pose a serious and complex challenge to global public health.[36,37]

Mortality rates

In North America, illegally manufactured fentanyl and other synthetic opioids have significantly contributed to a rapidly worsening disease burden of the 'opioid overdose crisis'.[38–40] A 'triple wave' of opioid deaths in the United States has been reported, with an increase in mortality related to prescription opioids in the late 1990s, a rapid increase in heroin-related deaths beginning in 2010, followed by fentanyl and other synthetic opioids from 2014 onwards.[32,41] These are not discrete waves, but overlie each other and all contribute to the overall deaths within each wave. The Centers for Disease Control and Prevention (CDC) reported that 100,306 total drug overdose deaths occurred in the 12 months to April 2021 in the United States, and that synthetic opioids were the main cause of these deaths (75,673; 75.4%). In Canada, 7224 opioid-related deaths were reported in the 12 months to March 2021, an increase of 95%, with the large majority involving fentanyl or other synthetic opioids.[42–44] The UK Advisory Council on the Misuse of Drugs (ACMD) also published their report on synthetic opioids during the same time,[45] highlighting that the rates of drug-related deaths had steadily increased over the past decade, and that those related to novel synthetic opioids were likely to be under represented, due to the lack of available detailed forensic analyses. However, in the United Kingdom, the proportion of deaths related to fentanyl and new synthetic opioids is reported to be much lower than in North America. For example, 2020 death registrations estimate there were 60 fentanyl, fentanyl analogue or new synthetic opioid-related deaths, compared with 1337 heroin and morphine-related deaths.

International response

In response to an emerging global public health crisis, the United Nations Office on Drugs and Crime (UNODC) launched an integrated strategy in 2018 to support countries in addressing the ongoing global synthetic opioids issue, which included coordinating the international response, reducing supply through changes in the scope of control of substances, and promoting effective prevention strategies and treatment options for

substance use disorders.[46] In addition to traditional prevention and treatment responses, strategies proposed by other policymakers, organisations, and researchers in markets with high risk of exposure to new opioids include the expansion of supervised drug consumption facilities; increased coverage of an expanded set of opioid agonist therapies; and the introduction of community-based 'drug checking' that would provide rapid information on circulating substances in a local market.[42]

Appearance of new synthetic opioids

In 2020, the UNODC reported that the number of new synthetic illicitly manufactured opioids identified annually had increased significantly from just one in 2009 to 55 in 2018.[47] In addition, they reported that between 2015 and 2019, the number of synthetic opioids, as a proportion of NPS, quadrupled from 2% to 8%.[48] The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) reported similar findings, and since 2009 a total of 57 new synthetic opioids have been detected for the first time in Europe, including eight reported for the first time in 2019. In contrast to previous years, only two of these were fentanyl derivatives, the remaining six all being chemically distinct from fentanyl, despite posing similar concerns in respect to their toxicity, and they were termed non-fentanyl opioids.[49,50] In the United Kingdom, the ACMD concluded that synthetic opioids posed a significant risk to public health and recommended that current monitoring and surveillance systems be adapted to help identify the true scale of the public health threat.[51]

Emerging markets

Synthetic opioids are sold not only as standalone products but also as counterfeit opioid medications and may be adulterants in street-level supplies of controlled drugs such as heroin, cocaine and benzodiazepines.[52] Although some people will intentionally seek out these synthetic opioids, many are not aware of the constituent elements of what they have purchased and so can be unintentionally exposed to substances of unknown pharmacology and toxicity.[53] Although financial profit motivates production and distribution, research suggests reasons for emergence may differ among regional markets. In the United States, for example, analysis suggests that growth in synthetic opioid consumption arose after restrictions were placed on access to prescription opioids after the first wave of opioid deaths in the early 2000s, whereas in some European countries this was a result of heroin shortages.[42,50,52]

Mechanism of action

The endogenous opioid system consists of three opioid receptors: mu-, delta- and kappa-opioid receptors, all of which are 7-transmembrane domain, G-protein coupled inhibitory receptors. Mu-opioid receptors are expressed throughout the peripheral and central nervous system and are associated with analgesia and dependence formation, in addition to their euphoric, sedative and respiratory depressant effects and constipation.[54,55] Agonism [the combining of a chemical substance (such as a drug) with a specific receptor on a cell thereby initiating the same reaction or activity typically produced by the binding of an endogenous substance] at both delta- and kappa-opioid receptors is also associated with analgesia,[55,56] and additionally, agonism at kappa-opioid receptors is responsible for the dysphoric effects of opioids, which may also contribute partly to dependence formation.[55,57] Expression of opioid receptors in humans is most concentrated within the limbic system, hypothalamus, caudate nuclei, periaqueductal grey, dorsal horn of the spinal cord and dorsal root ganglia, and they are found on both pre- and post-synaptic membranes.[56,58] At the spinal level, opioid receptors work to inhibit afferent nociceptive signalling from the dorsal horn.[56] Observations of opioid receptors expressed on peripheral sensory neurons, and the effectiveness of peripherally administered opioid analgesia, support the notion that peripheral opioid receptors play an important role in pain perception following injury.[59,60]

The four canonical endogenous opioid receptor ligands are beta-endorphin, leu-enkephalin, met-enkephalin and dynorphin. These ligands are agonists at opioid receptors, each with varying affinities to the three opioid receptor subtypes: beta-endorphin notably acting as a full-agonist of all three opioid receptors, whereas the enkephalins show a relatively higher affinity for delta-opioid receptors, and dynorphin shows a higher affinity for kappa-opioid receptors.[58]

Stimulation of the mu-opioid receptor promotes the exchange of guanosine triphosphate (GTP) for guanosine diphosphate (GDP) in the G-protein complex, which then inhibits adenylate

cyclase in the cells causing a decrease in intracellular cyclic adenosine monophosphate (cAMP).[61] The activation of the mu-opioid receptors also inhibits calcium and potassium ion channel conductance.[62] These events lead to neuronal membrane hyperpolarisation and inhibition of tonic neural activity, and subsequent reduction of the release of several neurotransmitters (including acetylcholine, noradrenaline, substance P, GABA, and dopamine).[63]

Synthetic opioids stimulate limbic and midbrain dopaminergic circuitry, thought to underpin the euphoric effect sought by users, in addition to also causing depressant effects such as analgesia, sedation, and a reduction in consciousness level.[64,65] Direct stimulation of the chemoreceptor trigger zone in the area postrema may cause nausea and vomiting.[66] The toxicity associated with synthetic opioids relates partly to their high affinity for the mu-opioid receptors and their lipophilicity,[67–69] which can result in the development of opioid toxicity at very low doses.

Mode of use and clinical presentation
Synthetic opioids are manufactured in powder, tablet (including lozenges), transdermal patch and liquid forms and can be consumed by swallowing, nasal insufflation (snorting), smoking, injecting, transdermal application, or application sublingually, vaginally or rectally. Reported novel ways of consuming these compounds include inhaling using electronic nicotine delivery (vaping) devices. The absorption of synthetic opioids from swallowed transdermal patches can be increased by chewing prior to swallowing. In addition, they can be extracted from transdermal patches for use by alternative routes such injection or nasal insufflation, as the patches retain a large amount of drug even after they have been used therapeutically.[70,71] Similar to other natural and semi-synthetic opioid use, the main desired effects are relaxation, euphoria and analgesia, but synthetic opioids produce significant inter-individual dose/response variability leading to different toxic doses and clinical presentations.[72,73] Synthetic opioid affects all the major biological systems, producing effects including nausea, vomiting, bradycardia, hypotension, constipation, weight loss, chest pain, hypoxia, pulmonary oedema and cyanosis.[74–76] The most common adverse neurological effect is a reduced level of consciousness.[77] People who have consumed novel non-fentanyl compounds present with a wide range of non-opioid expected adverse effects including paraesthesia, limb weakness, balance disturbance, visual and hearing impairments and skin rashes.[78,79]

Compound-specific chemical structure
Synthetic opioids include fentanyl (discovered in 1959)[27] and its analogues used in medical therapy, sufentanil (1974),[80] alfentanil (1976)[81] and remifentanil (1987).[82] Those fentanyls not approved for human medical use are sometimes described as non-pharmaceutical fentanyls and include acetylfentanyl (1962),[83] carfentanil (1974),[84] ocfentanil (1984)[85] and furanylfentanyl (1986).[86] New synthetic opioids chemically unrelated to fentanyl (non-fentanyl compounds) have emerged on the global drugs market since 2010 and include MT-45 [1-cyclohexyl-4-(1,2-diphenylethyl) piperazine], AH-7921 [3,4-dichloro-N-{[1(dimethylamino) cyclohexyl]methyl} benzamide] andU-47700[3,4-dichloro-N-[(1R,2R)-2-(dimethylamino) cyclohexyl]-N-methylbenzamide].[72,87–89] Table 1 outlines synthetic opioids, their receptor affinity and potency related to morphine. We now describe some of the more commonly available synthetic opioids, in terms of their pharmacological profiles and where appropriate, atypical unwanted effects reported to be associated with their use.

Fentanyl and its analogues
Fentanyl and its main analogues alfentanil, sufentanil, and remifentanil are used in surgery as adjuncts to anaesthesia, for sedation and the treatment of acute and chronic pain.[90] Fentanyl is a 2-phenylethyl-substituted 4-anilinopiperidine derivative carrying a propionylamide moiety linked to the aniline-nitrogen. There are four structural features which may be modified, resulting in a huge variety of fentanyl analogues: (a) the piperidine ring, (b) the anilinophenyl ring, (c) the 2-phenylethyl substituent, and (d) a carboxamide moiety linked to the anilino-nitrogen.[91–94]

Fentanyl [N-phenyl-N-[1-(2-phenylethyl) piperidin-4-yl] propanamide] is a lipophilic phenylpiperidine synthetic opioid, that selectively binds to the mu-receptor in the central nervous system.[27,92] Its highly lipophilic nature enables it to pass through the membranes easily (including the blood brain barrier) and be widely distributed within the body.[92] Bioavailability depends on the route of administration. Low oral bioavailability is observed for fentanyl, with intranasal and oral bioavailability being 89% and 50%, respectively.[93]

Table 1. Synthetic opioids.

Class	Drug name	Opioid receptor selectivity			Relative potency compared with morphine	Blood concentration found to be lethal (ng/ml)
		μ	κ	δ		
Fentanyl and pharmaceutical analogues	Fentanyl	+ + +			50–100	0.3–383
	Sufentanil	+ + +	+	+	1000–4000	27
	Alfentanil	+ + +			72	100–200
Illicit fentanyl analogues	Acetylfentanyl	+ + +			15.7	153–260
	Acrylfentanyl	+ + +			170	1.86 ± 3.08
	3-methyl-fentanyl	+ + +			48.5–569	0.3–1.9
	β-hydroxy-3-methyl-fentanyl	+ + +			6300	NA
	α-methyl-fentanyl	+ + +			56.9	3.1
	α-methyl-acetyl-fentanyl	+ + +			3.1	NA
	4-fluoro-fentanyl	+ + +			15.7	0.24 ± 0.21
	Butyr-fentanyl	+ + +			1.5–7	0.1–99
	Carfentanil	+ + +			10,000	0.1–4.9
	Isobutyrylfentanyl	+ + +			NA	NA
	Ocfentanil	+ + +			90	5.3–15.3
	Furanyl-fentanyl	+ + +			7	0.4–26
Non-fentanyl analogues	U-47000	+ + +			7.5	13.8–490
	AH-7921	+ + +	+		1–1.7	31–6600
	MT-45	+ + +	+	+	~1	8.3–1989

"+/++/+++" are markers of approximate increasing affinity for the relevant receptor subtype.

Sufentanil (N-[4-(methoxymethyl)-1-(2-thiophen-2-ylethyl)piperidin-4-yl]-N-phenylpropanamide] is also a phenylpiperidine synthetic opioid. It differs from fentanyl through the addition of a methoxymethyl group on the piperidine ring (which increases its potency and reduces the duration of action) and the replacement of the phenyl ring by thiophene.[80,93] It is highly selective for the mu-receptor site, and 5–15 times more potent than fentanyl.[94]

Alfentanil N-[1-[2-(4-ethyl-5-oxotetrazol-1-yl)ethyl]-4-(methoxymethyl)piperidin-4-yl]-N-phenylpropanamide is also a phenylpiperidine synthetic opioid. It had also been created by introduction of additional substituents into the fourth position of the piperidine ring of fentanyl, in this case with the introduction of a methoxymethyl group coupled with replacement of the phenyl ring of the phenethyl with a tetrazolyl ring.[30,95] While

not as potent as fentanyl, it is about 30 times more potent than morphine.[95] Compared with fentanyl and sufentanil, it has the most rapid analgesic onset and time to peak effect as well as the shortest distribution and elimination half-life, a small volume of distribution, greater binding to plasma proteins and less lipid solubility.[96,97]

Remifentanil {methyl1-(3-methoxy-3-oxopropyl)-4-[phenyl(propanoyl) amino]piperidine-4-carboxylate} was created by the replacement of the phenyl ring of the phenethyl group in the first position of piperidine ring with a substitution for a carbomethoxy group.[82] With an analgesic potency similar to fentanyl, it is metabolised directly in the plasma by non-specific esterases, an active group of enzymes found in blood and tissues throughout the body, resulting in an ultra-short duration of action.[98,99]

Non-pharmaceutical fentanyls

Carfentanil and ocfentanil are two potent synthetic opioids that have been implicated in the international opioid overdose crisis, particularly in the United States and some European countries.[100–103] Acetylfentanyl and furanylfentanyl have also recently been associated with cases of overdose and death in the United States.[104–111]

Carfentanil [methyl 1-(2-phenylethyl)-4-(N-propanoylanilino)-piperidine-4-carboxylate] is a member of the N-4 substituted fentanyl analogues, carrying an additional methyl-carboxylate moiety at the 4-position of the piperidine ring. It is one of the most potent opioids and is approved for use in veterinary medicine only as a general anaesthetic agent or as a tranquillising agent for large animals such as elephants, as its extreme potency makes it inappropriate for use in humans. It has a quantitative potency approximately 10,000 times that of morphine and 100 times that of fentanyl.[68,108,112,113] Carfentanil is a very potent agonist at all opioid receptors but acts primarily on the mu-opioid receptor subtype. Carfentanil has been found to be mis-sold as other drugs, including heroin, or used as a substitute to reportedly increase profitability, leading to hundreds of opioid overdoses, many of them fatal. It is the most potent opioid present in the controlled market at present.[114–116]

Ocfentanil [N-(2-fluorophenyl)-2-methoxy-N-[1-(2-phenylethyl)-piperidin-4-yl] acetamide possesses a methoxy group instead of a methyl group and a fluorine atom on the ortho position of the aniline group.[117] Ocfentanil was found to be 2.5 times as potent as fentanyl and around 200 times as potent as morphine.[118] Ocfentanil was never developed for pharmaceutical use and was detected on the controlled drug market after 2010.[114]

Acetylfentanyl [N-Phenyl-N-[1-(2-phenylethyl)-4-piperidinyl] acetamide] is the acetyl amide analogue of fentanyl with a substitution of the N-propionyl moiety for an acetyl moiety.[119] It demonstrates some similarities with heroin such as colour, consistency and pharmacologic activity and is around 15 times more potent than morphine, but it has 3 times lower potency than fentanyl.[120,121] Reports have suggested the use of propylene glycol electronic cigarettes filled with acetylfentanyl, as well as its mixture with alcoholic beverages as innovative methods for consumption.[122,123]

Furanylfentanyl [N-(1-(2-phenylethyl)-4-piperidinyl)-N-phenyl-furan-2-carboxamide] has a furanyl ring in place of the methyl group adjacent to the carbonyl bridge and has a comparable potency to fentanyl.[124] In a study into fentanyl and analogue-related deaths across five counties in New York between 2013 and 2017, 417 deaths were found to have been reported, increasing from 10 cases in 2013 to 184 cases in 2017 and that furanylfentanyl was one of the common drugs involved.[125]

Non-fentanyl opioids

Since 2010, a new generation of synthetic opioids, structurally different from fentanyl, have emerged on the recreational drug market. Their chemical structures belong to benzamide (U-47700, U-48800 or AH-7921), acetamide (U-50488, U-51754) or piperazine (MT-45) classes of compounds.[108]

U-47700 [3,4-dichloro-N-[(1R,2R)-2-(dimethylamino)cyclohexyl]-N-methylbenzamide] is a structural isomer of AH-7921. Slang terms include 'fake morphine' or 'U4'and is sometimes referred to as 'pink', because of impurities during its production cause the constituent powder to be pink in colour.[126] It is 7.5 times more potent than morphine, with an affinity for the mu-opioid receptor,[127,128] and has been associated with recent intoxication cases and deaths in the United States.[129–132]

U-50488 [trans-3,4-dichloro-N-methyl-N-[2-(1-pyrrolidinyl) cyclohexyl]-benzeneacetamide] is a kappa-opioid receptor agonist, with some reported mu-opioid receptor respiratory antagonist

effects.[124,133] Studies in animals have shown that U-50488 causes diuresis and dysphoria rather than respiratory depression or constipation.[134] The toxicological profile of U-50488 currently remains under research, but the structural similarity to U-47700 suggests that it might pose a significant risk.[135]

MT-45 [1-cyclohexyl-4-(1,2-diphenylethyl)piperazine] is structurally distinct from other therapeutic opioids and demonstrates selective mu-opioid receptor agonism, with considerably lower delta- and kappa-opioid receptor affinities, and with similar potency to morphine.[136,137] Reported adverse effects include hair depigmentation and loss, hearing loss, folliculitis, dermatitis, disorganised keratinisation, and bilateral secondary cataracts requiring surgery.[138,139] MT-45 has been associated with reports of fatal intoxications in Europe.[140] In Sweden, it was been associated with 28 analytically confirmed deaths between November 2013 and July 2014.[141]

Management of acute toxicity and overdose

Clinical features
Fentanyl and its analogues have a high affinity for mu-opioid receptors, which account for the central nervous system and respiratory depression associated with their significant morbidity and mortality.[142] Typical symptoms seen in an overdose are miosis ('pinpoint pupils'), respiratory depression, and a decreased level of consciousness or coma. This is known as the 'opioid overdose triad'.[143] In severe opioid toxicity, this can lead to respiratory arrest and death. Vomiting in the setting of reduced unconsciousness and/or protective airway reflexes can increase the risk of aspiration. Therefore, loss of protective airway reflexes and/or significant central nervous system depression which doesn't respond to antidote therapy can necessitate intubation for airway protection. Prolonged admission to intensive care for ongoing management has been reported, in part due to the pharmacokinetic properties of some of these synthetic opioids and their longer duration of action.[144,145] Other reported unwanted effects seen with synthetic opioids include alterations in muscle tone, chest wall rigidity, 'seizure-like' activity, confusion, affective changes, cough suppression, orthostatic hypotension, urinary urgency or retention, folliculitis and dermatitis with hair loss, dry eyes, elevated liver enzymes and delayed bilateral hearing loss.[70,71,78] Nasal burn or nasal drip after insufflation and a bitter taste after oral

ingestion have been reported; these effects are commonly seen with a range of NPS including non-opioid NPS.[64]

Clinical management
During an overdose, there is a sustained effect on the brainstem and cortical centres regulating respiratory rate, resulting in respiratory depression and potentially death.[146] Initial management should focus on protecting the airway and maintaining breathing and circulation as in any emergency situation.[147–149] Naloxone is a competitive mu-opioid receptor antagonist, which reverses central and peripheral opioid effects rapidly. Naloxone can be administered *via* the intravenous, intramuscular, intranasal, intraosseous, subcutaneous, endotracheal, inhalational and sublingual routes.[150,151] It is recommended that where possible it is given intravenously, as this allows titration of dose to the desired clinical response while reducing the risk of unwanted effects such as acute withdrawal. In the prehospital setting or where intravenous access is not possible, then use by intramuscular injection would be appropriate, although there is greater potential for unwanted effects and acute withdrawal due to unpredictable absorption of the naloxone. There has been increasing interest in the use of intra-nasal naloxone in the prehospital setting to reduce the risk of needle-stick injuries related to intramuscular injection. The discussion of appropriate dosing regimens in different settings and/or patterns of acute toxicity is outside the scope of this review article, and we recommend that readers obtain this information from their local poisons centre or information services. However, it is worth noting that the high potency, rapid onset of action and relatively long half-life of synthetic opioids pose particular challenges for reversal by naloxone. Reports suggest that the management of a synthetic opioid overdose requires larger or more frequent repeated doses of naloxone than would normally be recommended.[152–157]

Dependence and withdrawal syndromes
Opioid dependence involves a cluster of symptoms, including impaired control over use, prominence of use of a substance in a person's life, and physiological symptoms such as tolerance and withdrawal.[39] It is best characterised as a typically chronic, relapsing condition with periods of active use, abstinence, and relapse over years or

decades.[158,159] Risk of mortality from overdose is increased when tolerance is reduced after a period of abstinence, such as imprisonment.[160–162] Available data suggest that repeated use of fentanyls and their analogues leads to the development of tolerance and dependence more rapidly than with natural or semi-synthetic opioids[163] and that non-fentanyl opioids are associated with the highest risk of all the synthetic opiods.[72,164,165] Typical withdrawal symptoms are similar to that of natural and semi-synthetic opioids and include involve sweating, anxiety, diarrhoea, bone pain, abdominal cramps, and shivers with 'goose flesh skin' appearance.[64,166] Restless legs syndrome and psychotic symptoms have been reported to be associated with synthetic opioid withdrawal.[167,168]

Structured drug treatment interventions (e.g. opioid agonist therapies, psychosocial interventions) are effective in treating opioid use disorders, and pharmacotherapies (e.g. methadone, buprenorphine) reduce the risk of all cause and drug poisoning mortality. Hence, creating opportunities for those who may be exposed to new opioids to access drug treatment is an essential component of a comprehensive strategic response to the emergence of these compounds.[169,170]

Laboratory testing

Analytical methods for the determination of synthetic opioids are of great importance, and there is a need to focus on identifying both the parent drug and metabolites and to correlate the results with clinical outcomes and intoxication symptoms.[171–173] The constant arrival of new synthetic opioids on the controlled drugs market presents an important challenge. Most of these new substances are not detected by routine screening and confirmation methods, and due to the low doses of the highly potent drugs, the concentrations expected in the biological samples are in the low ng to pg/ml or ng to pg/g range, requiring extremely sensitive methods of analysis.[174,175] Routine screening is not undertaken in clinical practice as the results do not change outcome and are not available in a timeframe to change the outcome.

Current robust methods to identify synthetic opioids, due to their enhanced sensitivity and specificity, include gas chromatography coupled with mass spectrometry (GC-MS) or liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS), which allow both qualitative and quantitative analyses in different biological matrices.[176–178] GC-MS has historically been the analyser of choice in toxicology and a gold-standard test for drug detection and quantification.[179] However, there are several limitations which include sample preparation that may require several post-extraction derivatisation steps after micro-extraction of the sample has taken place, and a limited capacity for detection of non-volatile or polar molecules, for example, in the context of excretion of hydrophilic metabolites in urine.[131,174,180–182] LC-MS/MS permits the analysis of polar molecules, with limited sample preparation steps and lower limits of detection, and is therefore prioritised for the analysis of synthetic opioids.[183,184]

Both GC-MS and LC-MS/MS require up-to-date reference libraries for identifying synthetic opioids and face challenges from the continuous emergence of new structural derivatives.[184] Recent advances in mass spectrometry have permitted the development of high resolution (LC-HRMS) methods, with both targeted and untargeted workflows for synthetic opioid identification.[185] High resolution mass spectrometry (time-of-flight, Orbitrap) offers potential advantages to identify unknown compounds without the availability of a reference standard, but this technology is not readily available in most forensic laboratories.[185]

Conclusion

The market in controlled drugs is dynamic and continuously and rapidly changing. NPS producers create new chemical variations offering dangerous new alternatives to drugs that have become restricted, in part so as to circumvent existing national and international drug controls.

The evolving international opioid overdose crisis poses a new threat to the global public health community through the emergence of new synthetic opioids. These substances are readily produced by clandestine laboratories, distributed internationally, acquired easily *via* Internet sites, cheap to purchase, potentially easier to transport than conventional illicit drugs, relatively easy to use and often undetectable by conventional testing techniques. Many of them are much more potent than existing available opioids which has contributed to the rise in severe morbidity and mortality rates observed with their use.

The major public health concern remains that often users are not aware that they are exposing themselves to these more potent opioids, due to their contamination of both opioid and non-opioid

controlled drugs. Current laboratory detection methods may not detect all novel synthetic opioids, and detection in healthcare settings is currently sub-optimal. Global public health systems need to coordinate their response and focus on monitoring and intelligence sharing, primary prevention, healthcare workforce preparation, harm reduction, treatment, and public safety, if opioid-related morbidity and mortality are to be successfully addressed.

Authors' note
The authors believe that words and language are important, and so to reflect this, the word 'illicit' has been changed to 'controlled' for the purposes of this review.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Author contributions
Abu Shafi: Conceptualization; Writing – original draft; Writing – review & editing.

Alex J. Berry: Writing – original draft; Writing – review & editing.

Harry Sumnall: Writing – original draft; Writing – review & editing.

David M. Wood: Writing – original draft; Writing – review & editing.

Derek K. Tracy: Writing – review & editing.

Competing interests
The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Drs David Wood and Derek Tracy are members of the Advisory Council on the Misuse of Drugs (ACMD), a report of which is referenced within this paper. Professor Harry Sumnall is a former member of the ACMD but is a co-opted member of the ACMD working group on Cannabis based products for medicinal use.

Availability of data and materials
Not applicable.

ORCID iD
Derek K. Tracy (iD) https://orcid.org/0000-0002-3609-9407

References

1. Shafi A, Berry AJ, Sumnall H, *et al.* New psychoactive substances: a review and updates. *Ther Adv Psychopharmacol* 2020; 10: 967197.

2. Kapoor L. *Opium poppy: botany, chemistry, and pharmacology*. Boca Raton, FL: CRC Press, 1995.

3. Beaudoin GA and Facchini PJ. Benzylisoquinoline alkaloid biosynthesis in opium poppy. *Planta* 2014; 240: 19–32.

4. McCann JD. Do no good: how controlled substance regulations prohibit the use of telemedicine to provide medication-assisted therapy for opioid use disorder. *Tulsa L Rev* 2020; 56: 313.

5. Brook K, Bennett J and Desai SP. The chemical history of morphine: an 8000-year journey, from resin to de-novo synthesis. *J Anesth Hist* 2017; 3: 50–55.

6. Ghelardini C, Mannelli LD and Bianchi E. The pharmacological basis of opioids. *Clin Case Min Bone Metab* 2015; 12: 219.

7. Rice KC. The development of a practical total synthesis of natural and unnatural codeine, morphine and thebaine. In: David Phillipson J, Roberts MF and Zenk MH (eds) *The chemistry and biology of isoquinoline alkaloids*. Berlin; Heidelberg: Springer, 1985, pp. 191–203.

8. Grabley S and Thiericke R (eds). *Drug discovery from nature*. Berlin; Heidelberg: Springer, 1998.

9. Sneader W. The discovery of heroin. *Lancet* 1998; 352: 1697–1699.

10. Hosztafi S. The history of heroin. *Acta Pharm Hung* 2001; 71: 233–242.

11. Fernandez H. *Heroin*. Minnesota, MN: Hazelden, 1998.

12. Ruan X, Mancuso KF and Kaye AD. Revisiting oxycodone analgesia: a review and hypothesis. *Anesthesiol Clin* 2017; 35: e163–e174.

13. Yarnell E. The botanical roots of pharmaceutical discovery. *Altern Complement Ther* 2000; 6: 125–128.

14. Vadivelu N, Maria M, Jolly S, *et al.* Clinical applications of oxymorphone. *J Opioid Manag* 2013; 9: 439–452.

15. Cicero TJ, Ellis MS, Surratt HL, *et al.* The changing face of heroin use in the United States: a retrospective analysis of the past 50 years. *JAMA Psychiat* 2014; 71: 821–826.

16. Büttner A, Mall G, Penning R, *et al.* The neuropathology of heroin abuse. *Forensic Sci Int* 2000; 113: 435–442.

17. Bull M. *Governing the heroin trade: from treaties to treatment*. New York: Routledge, 2016.

18. Carnwath T and Smith I. *Heroin century*. New York: Routledge, 2003.

19. Paoli L, Greenfield VA and Reuter P. *The world heroin market: can supply be cut?* New York: Oxford University Press, 2009.

20. Simmons LR and Gold MB. The myth of international control: American foreign policy and the heroin traffic. *Int J Addict* 1973; 8: 779–800.

21. Hall W. The future of the international drug control system and national drug prohibitions. *Addiction* 2018; 113: 1210–1223.

22. Morrison S. The dynamics of controlled drugs production: future sources and threats. *Crime Law Soc Change* 1997; 27: 121–138.

23. Storti CC and De Grauwe P. Globalization and the price decline of controlled drugs. *Int J Drug Policy* 2009; 20: 48–61.

24. Vandam L, Matias J, McKetin R, *et al.* Illicit drug trends globally. In: *International Encyclopedia of Public Health*. 2016, pp. 146–156. DOI: 10.1016/B978-0-12-803678-5.00223-X.

25. Ravina E. *The evolution of drug discovery: from traditional medicines to modern drugs*. New York: John Wiley & Sons, 2011.

26. Payte JT. A brief history of methadone in the treatment of opioid dependence: a personal perspective. *J Psychoactive Drugs* 1991; 23: 103–107.

27. Stanley TH. The history and development of the fentanyl series. *J Pain Symptom Manage* 1992; 7: S3–S7.

28. Haghighatnia Y, Balalaie S and Bijanzadeh HR. Designing and synthesis of novel amidated fentanyl analogs. *Helvet Chimi Acta* 2012; 95: 818–824.

29. Burns SM, Cunningham CW and Mercer SL. DARK classics in chemical neuroscience: fentanyl. *ACS Chem Neurosci* 2018; 9: 2428–2437.

30. Vardanyan RS and Hruby VJ. Fentanyl-related compounds and derivatives: current status and future prospects for pharmaceutical applications. *Future Med Chem* 2014; 6: 385–412.

31. Prekupec MP, Mansky PA and Baumann MH. Misuse of novel synthetic opioids: a deadly new trend. *J Addict Med* 2017; 11: 256–265.

32. Beletsky L and Davis CS. Today's fentanyl crisis: Prohibition's Iron Law, revisited. *Int J Drug Policy* 2017; 46: 156–159.

33. Manchikanti L, Sanapati J, Benyamin RM, *et al.* Reframing the prevention strategies of the opioid crisis: focusing on prescription opioids, fentanyl, and heroin epidemic. *Pain Phys* 2018; 21: 309–326.

34. Han Y, Yan W, Zheng Y, *et al.* The rising crisis of controlled fentanyl use, overdose, and potential therapeutic strategies. *Trans Psychiat* 2019; 9: 1–9.

35. Fischer B, Vojtila L and Rehm J. The 'fentanyl epidemic' in Canada: some cautionary observations focusing on opioid-related mortality. *Prev Med* 2018; 107: 109–113.

36. Al-Rawi A. The fentanyl crisis & the dark side of social media. *Telemat Inform* 2019; 45: 101280.

37. Socías ME and Wood E. Epidemic of deaths from fentanyl overdose. *BMJ* 2017; 358: j4355. DOI: 10.1136/bmj.j4355.

38. Zoorob M. Fentanyl shock: the changing geography of overdose in the United States. *Int J Drug Policy* 2019; 70: 40–46.

39. Degenhardt L, Grebely J, Stone J, *et al.* Global patterns of opioid use and dependence: harms to populations, interventions, and future action. *Lancet* 2019; 394(10208): 1560–1579.

40. Belzak L and Halverson J. The opioid crisis in Canada: a national perspective. *Health Promot Chronic Dis Prev Can* 2018; 38: 224–233.

41. Ciccarone D. The triple wave epidemic: supply and demand drivers of the US opioid overdose crisis. *Int J Drug Policy* 2019; 71: 183–188.

42. Pardo B, Taylor J, Caulkins J, *et al.* The dawn of a new synthetic opioid era: the need for innovative interventions. *Addiction* 2020; 16: 1304–1312.

43. Drug overdose deaths in the U.S. top 100,000 annually, https://www.cdc.gov/nchs/pressroom/nchs_press_releases/2021/20211117.htm

44. Opioid- and stimulant-related harms in Canada published: (September 2022), https://health-infobase.canada.ca/substance-related-harms/opioids-stimulants/

45. Reducing opioid-related deaths in the UK, https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/576560/ACMD-Drug-Related-Deaths-Report-161212.pdf (accessed 28 December 2020).

46. Wilson N, Kariisa M, Seth P, *et al.* Drug and opioid-involved overdose deaths: United States, 2017–2018. *Morb Mort Weekly Rep* 2020; 69: 290–297.

47. UNODC opioid strategy 2020, https://www.unodc.org/unodc/en/opioid-crisis/the-strategy.html (accessed 28 December 2020).

48. Global SMART update 2020, https://www.unodc.org/documents/scientific/Global_SMART_Update_2020-Vol.24-Eng-Final.pdf (accessed 28 December 2020).

49. United Nations world drug report 2020, https://wdr.unodc.org/wdr2020/ (accessed 28 December 2020).

50. European drug report 2020, https://www.emcdda.europa.eu/system/files/publications/13238/TD0420439ENN.pdf (accessed 28 December 2020).

51. Misuse of fentanyl and fentanyl analogues: ACMD report 2020, https://www.gov.uk/government/publications/misuse-of-fentanyl-and-fentanyl-analogues (accessed 28 December 2020).

52. Palamar JJ, Ciccarone D, Rutherford C, *et al.* Trends in seizures of powders and pills containing illicit fentanyl in the United States, 2018 through 2021. *Drug Alcohol Depend* 2022; 234: 109398.

53. Ciccarone D, Ondocsin J and Mars SG. Heroin uncertainties: exploring users' perceptions of fentanyl-adulterated and -substituted 'heroin'. *Int J Drug Policy* 2017; 46: 146–155.

54. Dorn S, Lembo A and Cremonini F. Opioid-induced bowel dysfunction: epidemiology, pathophysiology, diagnosis, and initial therapeutic approach. *Am J Gastroenterol Suppl* 2014; 2: 31.

55. Zöllner C and Stein C. Opioids. *Analgesia* 2006: 31–63.

56. Moy JK, Hartung JE, Duque MG, *et al.* Distribution of functional opioid receptors in human dorsal root ganglion neurons. *Pain* 2020; 161: 1636–1649.

57. Mysels D and Sullivan MA. The kappa-opiate receptor impacts the pathophysiology and behavior of substance use. *Am J Addict* 2009; 18: 272–276.

58. Pasternak GW and Pan YX. Mu opioids and their receptors: evolution of a concept. *Pharmacol Rev* 2013; 65: 1257–1317.

59. Mousa SA, Zhang Q, Sitte N, *et al.* β-Endorphin-containing memory-cells and μ-opioid receptors undergo transport to peripheral inflamed tissue. *J Neuroimmunol* 2001; 115: 71–78.

60. Tegeder I, Meier S, Burian M, *et al.* Peripheral opioid analgesia in experimental human pain models. *Brain* 2003; 126: 1092–1102.

61. Foley KM. Opioids and chronic neuropathic pain. *N Engl J Med* 2003; 348: 1279.

62. Vaughan CW, Ingram SL, Connor MA, *et al.* How opioids inhibit GABA-mediated neurotransmission. *Nature* 1997; 390: 611–614.

63. Horsfall JT and Sprague JE. The pharmacology and toxicology of the 'holy rrinity'. *Basic Clin Pharmacol Toxicol* 2017; 120: 115–119.

64. Suzuki J and El-Haddad S. A review: fentanyl and non-pharmaceutical fentanyls. *Drug Alcohol Depend* 2017; 171: 107–116.

65. Mounteney J, Giraudon I, Denissov G, *et al.* Fentanyls: are we missing the signs? Highly potent and on the rise in Europe. *Int J Drug Policy* 2015; 26: 626–631.

66. Brunton LL, Chabner BA and Knollmann BC. Pharmacotherapy of the epilepsies. In: McNamara JO (ed.) *Goodman & Gilman's the pharmacological basis of therapeutics*. 12th ed. Valproic Acid, 2011, https://accessmedicine.mhmedical.com/content.aspx?bookid=1613&sectionid=102159324#:~:text=Carbamazepine%2C%20lamotrigine%2C%20phenytoin%2C%20and,Rogawski%20and%20Loscher%2C%202004)

67. Concheiro M, Chesser R, Pardi J, *et al.* Postmortem toxicology of new synthetic opioids. *Front Pharmacol* 2018; 9: 1210.

68. Leen JL and Juurlink DN. Carfentanil: a narrative review of its pharmacology and public health concerns. *Can J Anesth/J Can d'Anesth* 2019; 66: 414–421.

69. Armenian P, Vo KT, Barr-Walker J, *et al.* Fentanyl, fentanyl analogues and novel synthetic opioids: a comprehensive review. *Neuropharmacology* 2018; 134: 121–132.

70. Siddiqi S, Verney C, Dargan P, *et al.* Understanding the availability, prevalence of use, desired effects, acute toxicity and

dependence potential of the novel opioid MT-45. *Clin Toxicol* 2015; 53: 54–59.

71. Helander A, Bradley M, Hasselblad A, *et al.* Acute skin and hair symptoms followed by severe, delayed eye complications in subjects using the synthetic opioid MT-45. *Br J Dermatol* 2017; 176: 1021–1027.

72. Beardsley PM and Zhang Y. Synthetic opioids. *New Psycho Subst* 2018: 252: 353–381.

73. Karila L, Marillier M, Chaumette B, *et al.* New synthetic opioids: part of a new addiction landscape. *Neurosci Biobehav Rev* 2019; 106: 133–140.

74. Fischer B, Jones W, Tyndall M, *et al.* Correlations between opioid mortality increases related to controlled/synthetic opioids and reductions of medical opioid dispensing-exploratory analyses from Canada. *BMC Public Health* 2020; 20: 1–7.

75. Kuczyńska K, Grzonkowski P, Kacprzak Ł, *et al.* Abuse of fentanyl: an emerging problem to face. *Forensic Sci Int* 2018; 289: 207–214.

76. Kuhlman JJ Jr, McCaulley R, Valouch TJ, *et al.* Fentanyl use, misuse, and abuse: a summary of 23 postmortem cases. *J Anal Toxicol* 2003; 27: 499–504.

77. Benyamin R, Trescot AM, Datta S, *et al.* Opioid complications and side effects. *Pain Phys* 2008; 11: S105–20.

78. Helander A, Bäckberg M and Beck O. MT-45, a new psychoactive substance associated with hearing loss and unconsciousness. *Clin Toxicol* 2014; 52: 901–904.

79. Comer SD and Cahill CM. Fentanyl: receptor pharmacology, abuse potential, and implications for treatment. *Neurosci Biobehav Rev* 2019; 106: 49–57.

80. Maciejewski D. Sufentanil in anaesthesiology and intensive therapy. *Anaesthesiol Intensive Ther* 2012; 44: 35–41.

81. Janssens F, Torremans J and Janssen PA. Synthetic 1, 4-disubstituted 1, 4-dihydro-5H-tetrazol-5-one derivatives of fentanyl: alfentanil (R 39209), a potent, extremely short-acting narcotic analgesic. *J Med Chem* 1986; 29: 2290–2297.

82. Feldman PL. Insights into the chemical discovery of remifentanil. *Anesthesiology* 2020; 132: 1229–1234.

83. Janssen PA and van der Eycken CA. The chemical anatomy of potent morphine-like analgesics. *Drugs Affect Centr Nerv Syst* 1968; 2: 25.

84. Ringuette AE, Spock M, Lindsley CW, *et al.* DARK classics in chemical neuroscience: carfentanil. *ACS Chem Neurosci* 2020; 11: 3955–3967.

85. Huang BS, Terrell RC, Deutsche KH, *et al.* N-aryl-N-(4-piperidinyl) amides and pharmaceutical compositions and method employing such compounds. Patent US 4584303, USA, 1986.

86. Misailidi N, Papoutsis I, Nikolaou P, *et al.* Furanylfentanyl: another fentanyl analogue, another hazard for public health. *Forensic Toxicol* 2018; 36: 1.

87. Lemmens HJ. Pharmacokinetic-pharmacodynamic relationships for opioids in balanced anaesthesia. *Clin Pharmacokinet* 1995; 29: 231–242.

88. Fels H, Krueger J, Sachs H, *et al.* Two fatalities associated with synthetic opioids: AH-7921 and MT-45. *Forensic Sci Int* 2017; 277: e30–e35.

89. Schneir A, Metushi IG, Sloane C, *et al.* Near death from a novel synthetic opioid labeled U-47700: emergence of a new opioid class. *Clin Toxicol* 2017; 55: 51–54.

90. Zawilska JB. An expanding world of novel psychoactive substances: opioids. *Front Psychiatry* 2017; 8: 110.

91. Peng PW and Sandler AN. A review of the use of fentanyl analgesia in the management of acute pain in adults. *Anesthesiology* 1999; 90: 576–599.

92. Vuckovic S, Prostran M, Ivanovic M, *et al.* Fentanyl analogs: structure-activity-relationship study. *Curr Med Chem* 2009; 16: 2468–2474.

93. Casy AF and Huckstep MR. Structure-activity studies of fentanyl. *J Pharm Pharmacol* 1988; 40: 605–608.

94. Higashikawa Y and Suzuki S. Studies on 1-(2-phenethyl)-4-(N-propionylanilino) piperidine (fentanyl) and its related compounds. VI. Structure-analgesic activity relationship for fentanyl, methyl-substituted fentanyls and other analogues. *Forensic Toxicol* 2008; 26: 1–5.

95. Black TE, Kay B and Healy TE. Reducing the haemodynamic responses to laryngoscopy and intubation: a comparison of alfentanil with fentanyl. *Anaesthesia* 1984; 39: 883–887.

96. Camu F, Gepts E, Rucquoi M, *et al.* Pharmacokinetics of alfentanil in man. *Anesth Anal* 1982; 61: 657–661.

97. Stanski DR and Hug CC Jr. Alfentanil: a kinetically predictable narcotic analgesic. *Anesthesiology* 1982; 57: 435–438.

98. Rosow CE. An overview of remifentanil. *Anesth Anal* 1999; 89: 1.

99. Scott LJ and Perry CM. Remifentanil. *Drugs* 2005; 65: 1793–1823.

100. Misailidi N, Papoutsis I, Nikolaou P, *et al.* Fentanyls continue to replace heroin in the drug arena: the cases of ocfentanil and carfentanil. *Forensic Toxicol* 2018; 36: 12–32.

101. Soelberg CD, Brown RE Jr, Du Vivier D, *et al.* The US opioid crisis: current federal and state legal issues. *Anesth Analg* 2017; 125: 1675–1681.

102. Hernandez A, Branscum AJ, Li J, *et al.* Epidemiological and geospatial profile of the prescription opioid crisis in Ohio, United States. *Sci Rep* 2020; 10: 1.

103. Jalal H and Burke DS. Carfentanil and the rise and fall of overdose deaths in the United States. *Addiction* 2021; 116: 1593–1599.

104. Cunningham SM, Haikal NA and Kraner JC. Fatal intoxication with acetyl fentanyl. *J Forensic Sci* 2016; 61: S276–S280.

105. Fort C, Curtis B, Nichols C, *et al.* Acetyl fentanyl toxicity: two case reports. *J Anal Toxicol* 2016; 40: 754–757.

106. Stogner JM. The potential threat of acetyl fentanyl: legal issues, contaminated heroin, and acetyl fentanyl 'disguised' as other opioids. *Ann Emerg Med* 2014; 64: 637–639.

107. Ogilvie L, Stanley C, Lewis L, *et al.* Acetyl fentanyl overdose fatalities: Rhode Island, March–May 2013. *Morb Mort Weekly Rep* 2013; 62: 703.

108. O'Donnell JK, Halpin J, Mattson CL, *et al.* Deaths involving fentanyl, fentanyl analogs, and U-47700: 10 states, July–December 2016. *Morb Mort Weekly Rep* 2017; 66: 1197.

109. Daniulaityte R, Juhascik MP, Strayer KE, *et al.* Overdose deaths related to fentanyl and its analogs: Ohio, January–February 2017. *Morb Mort Weekly Rep* 2017; 66: 904.

110. Daniulaityte R, Juhascik MP, Strayer KE, *et al.* Trends in fentanyl and fentanyl analogue-related overdose deaths: Montgomery County, Ohio, 2015–2017. *Drug Alcohol Depend* 2019; 198: 116–120.

111. Guerrieri D, Rapp E, Roman M, *et al.* Postmortem and toxicological findings in a series of furanylfentanyl-related deaths. *J Anal Toxicol* 2017; 41: 242–249.

112. George AV, Lu JJ, Pisano MV, *et al.* Carfentanil: an ultra potent opioid. *Am J Emerg Med* 2010; 28: 530–532.

113. Fomin D, Baranauskaite V, Usaviciene E, *et al.* Human deaths from drug overdoses with carfentanyl involvement – new rising problem in forensic medicine: a STROBE-compliant retrospective study. *Medicine* 2018; 97: e13449.

114. Massey J, Kilkenny M, Batdorf S, *et al.* Opioid overdose outbreak: West Virginia, August 2016. *Morb Mort Weekly Rep* 2017; 66: 975.

115. Shanks KG and Behonick GS. Detection of carfentanil by LC-MS-MS and reports of associated fatalities in the USA. *J Anal Toxicol* 2017; 41: 466–472.

116. Swanson DM, Hair LS, Rivers Strauch SR, *et al.* Fatalities involving carfentanil and furanyl fentanyl: two case reports. *J Anal Toxicol* 2017; 41: 498–502.

117. Filer CN, Nugent RP and Huang BS. The synthesis of [fluorophenyl-3H (N)] ocfentanil and [fluorophenyl-3H (N)] brifentanil. *J Label Comp Radiopharm* 1995; 36: 1019–1027.

118. Dussy FE, Hangartner S, Hamberg C, *et al.* An acute ocfentanil fatality: a case report with post-mortem concentrations. *J Anal Toxicol* 2016; 40: 761–766

119. Krotulski AJ, Papsun DM, Friscia M, *et al.* Fatality following ingestion of tetrahydrofuranylfentanyl, U-49900 and methoxy-phencyclidine. *J Anal Toxicol* 2018; 42: e27–e32.

120. Evans-Brown M and Sedefov R. Responding to new psychoactive substances in the European Union: early warning, risk assessment, and control measures. *Handb Exp Pharmacol* 2018; 252: 3–49.

121. Melent'ev AB, Kataev SS and Dvorskaya ON. Identification and analytical properties of acetyl fentanyl metabolites. *J Anal Chem* 2015; 70: 240–248.

122. Rogers JS, Rehrer SJ and Hoot NR. Acetylfentanyl: an emerging drug of abuse. *J Emerg Med* 2016; 50: 433–436.

123. Lozier MJ, Boyd M, Stanley C, *et al.* Acetyl fentanyl, a novel fentanyl analog, causes 14 overdose deaths in Rhode Island, March–May 2013. *J Med Toxicol* 2015; 11: 208–217.

124. Mohr AL, Friscia M, Papsun D, *et al.* Analysis of novel synthetic opioids U-47700, U-50488 and furanyl fentanyl by LC–MS/MS in postmortem casework. *J Anal Toxicol* 2016; 40: 709–717.

125. Vohra V, Hodgman M, Marraffa J, *et al.* Fentanyl-and fentanyl analog-related deaths across five counties in Central New York

between2013 and 2017. *Clin Toxicol* 2020; 5858: 112–116.

126. Cheney BV, Szmuszkovicz J, Lahti RA, *et al.* Factors affecting binding of trans-N-[2-(methylamino) cyclohexyl] benzamides at the primary morphine receptor. *J Med Chem* 1985; 28: 1853–1864.

127. Narita M, Imai S, Itou Y, *et al.* Possible involvement of μ1-opioid receptors in the fentanyl-or morphine-induced antinociception at supraspinal and spinal sites. *Life Sci* 2002; 70: 2341–2354.

128. Elliott SP, Brandt SD and Smith C. The first reported fatality associated with the synthetic opioid 3, 4-dichloro-N-[2-(dimethylamino) cyclohexyl]-N-methylbenzamide (U-47700) and implications for forensic analysis. *Drug Test Anal* 2016; 8: 875–879

129. Ruan X, Chiravuri S and Kaye AD. Comparing fatal cases involving U-47700. *Forensic Sci Med Pathol* 2016; 12: 369–371.

130. Jones MJ, Hernandez BS, Janis GC, *et al.* A case of U-47700 overdose with laboratory confirmation and metabolite identification. *Clin Toxicol* 2017; 55: 55–59.

131. Gerace E, Salomone A and Vincenti M. Analytical approaches in fatal intoxication cases involving new synthetic opioids. *Curr Pharm Biotechnol* 2018; 19: 113–123.

132. Watanabe S, Vikingsson S, Roman M, *et al.* In vitro and in vivo metabolite identification studies for the new synthetic opioids acetylfentanyl, acrylfentanyl, furanylfentanyl, and 4-fluoro-isobutyrylfentanyl. *AAPS J* 2017; 19: 1102–1122.

133. Vonvoigtlander PF, Lahti RA and Ludens JH. U-50,488: a selective and structurally novel non-Mu (kappa) opioid agonist. *J Pharmacol Exp Ther* 1983; 224: 7–12.

134. Amin ZM, Rambaran KA, Fleming SW, *et al.* Addressing hazards from unscheduled novel psychoactive substances as research chemicals: the case of U-50488. *Cureus* 2017; 9: e1914.

135. Szmuszkovicz J. U-50,488 and the κ receptor: a personalized account covering the period 1973 to 1990. *Prog Drug Res* 1999; 52: 167–195.

136. Cannaert A, Hulpia F, Risseeuw M, *et al.* Report on a new opioid NPS: chemical and in vitro functional characterization of a structural isomer of the MT-45 derivative diphenpipenol. *J Anal Toxicol* 2021; 45: 134–140.

137. Coppola M and Mondola R. MT-45: a new, dangerous legal high. *J Opioid Manag* 2014; 10: 301–302.

138. Lindeman E, Bäckberg M, Personne M, *et al.* MT-45: a dangerous and potentially ototoxic internet drug. *Lakartidningen* 2014; 111: 1712–1715.

139. EMCDDA: Europol joint report on a new psychoactive substance: 1-cyclohexyl-4-(1,2-diphenylethyl)piperazine ('MT-45') [risk assessment report], September 2014, http://www.emcdda.europa.eu/publications/joint-reports/MT-45 (accessed 10 January 2021).

140. Bradley M, Hasselblad A, Norlen L, *et al.* Acute cutaneous symptom complex with subsequent cataract: the Internet drug MT-45 may be the cause. *Lakartidningen* 2016; 113, https://pubmed.ncbi.nlm.nih.gov/26835687/

141. Lucyk SN and Nelson LS. Novel synthetic opioids: an opioid epidemic within an opioid epidemic. *Ann Emerg Med* 2017; 69: 91–93.

142. Nelson L and Schwaner R. Transdermal fentanyl: pharmacology and toxicology. *J Med Toxicol* 2009; 5: 230–241.

143. Schiller EY, Goyal A and Mechanic OJ. Opioid overdose. In StatPearls [Internet] 2022. StatPearls Publishing, Treasure Island, FL.

144. Kumar K, Morgan DJ and Crankshaw DP. Determination of fentanyl and alfentanil in plasma by high-performance liquid chromatography with ultraviolet detection. *J Chrom B: Biomed Sci Appl* 1987; 419: 464–468.

145. Tomassoni AJ, Hawk KF, Jubanyik K, *et al.* Multiple fentanyl overdoses: New Haven, Connecticut, June 23, 2016. *Morb Mort Weekly Rep* 2017; 66: 107.

146. Pattinson KTS, Governo RJ, Macintosh BJ, *et al.* Opioids depress cortical centers responsible for the volitional control of respiration. *J Neurosci* 2009; 29: 8177–8186.

147. Parthvi R, Agrawal A, Khanijo S, *et al.* Acute opiate overdose: an update on management strategies in emergency department and critical care unit. *Am J Ther* 2019; 26: e380–e387

148. Chen Y, Wang Y, Nielsen S, *et al.* A systematic review of opioid overdose interventions delivered within emergency departments. *Drug Alcohol Depend* 2020; 213: 108009.

149. Houry DE, Haegerich TM and Vivolo-Kantor A. Opportunities for prevention and intervention of opioid overdose in the emergency department. *Ann Emerg Med* 2018; 71: 688–690.

150. Morgan J and Jones AL. The role of naloxone in the opioid crisis. *Toxicol Commun* 2018; 2: 15–18.

151. Moss RB and Carlo DJ. Higher doses of naloxone are needed in the synthetic opioid era. *Subst Abuse Treat Prev Policy* 2019; 14: 1–6.

152. Fairbairn N, Coffin PO and Walley AY. Naloxone for heroin, prescription opioid, and controlledly made fentanyl overdoses: challenges and innovations responding to a dynamic epidemic. *Int J Drug Policy* 2017; 46: 172–179.

153. Skolnick P. On the front lines of the opioid epidemic: rescue by naloxone. *Eur J Pharmacol* 2018; 835: 147–153.

154. Bell A, Bennett AS, Jones TS, *et al.* Amount of naloxone used to reverse opioid overdoses outside of medical practice in a city with increasing controlledly manufactured fentanyl in controlled drug supply. *Subst Abuse* 2018; 40: 52–55.

155. Baumann MH, Kopajtic TA and Madras BK. Pharmacological research as a key component in mitigating the opioid overdose crisis. *Trends Pharmacol Sci* 2018; 39: 995–998.

156. Jozaghi E, Maynard R, Dadakhah-Chimeh Z, *et al.* The synthetic opioid epidemic and the need for mental health support for first responders who intervene in overdose cases. *Can J Publ Health* 2018; 109: 231–232.

157. Bessen S, Metcalf SA, Saunders EC, *et al.* Barriers to naloxone use and acceptance among opioid users, first responders, and emergency department providers in New Hampshire, USA. *Int J Drug Policy* 2019; 74: 144–151.

158. Milone MC. Laboratory testing for prescription opioids. *J Med Toxicol* 2012; 8: 408–416.

159. Sordo L, Barrio G, Bravo MJ, *et al.* Mortality risk during and after opioid substitution treatment: systematic review and meta-analysis of cohort studies. *Bmj* 2017; 357: j1550.

160. Merrall EL, Kariminia A, Binswanger IA, *et al.* Meta-analysis of drug-related deaths soon after release from prison. *Addiction* 2010; 105: 1545–1554.

161. Kimber J, Larney S, Hickman M, *et al.* Mortality risk of opioid substitution therapy with methadone versus buprenorphine: a retrospective cohort study. *Lancet Psychiatry* 2015; 2: 901–908.

162. Cerdá M, Santaella J, Marshall BD, *et al.* Nonmedical prescription opioid use in childhood and early adolescence predicts transitions to heroin use in young adulthood: a national study. *J Pediatr* 2015; 167: 605–612.

163. Eiden C, Mathieu O, Donnadieu-Rigole H, *et al.* High opioids tolerance due to transmucosal fentanyl abuse. *Eur J Clin Pharmacol* 2017; 73: 1195–1196.

164. Peppin JF, Raffa RB and Schatman ME. The polysubstance overdose-death crisis. *J Pain Res* 2020; 13: 3405–3408.

165. Peppin JF, Pergolizzi JV Jr, Vortsman E, *et al.* Commentary: 'Ockham's Razor' doesn't apply to 'opioid' overdose death. *J Biosci Med* 2021; 9: 98.

166. Pérez-Mañá C, Papaseit E, Fonseca F, *et al.* Drug interactions with new synthetic opioids. *Front Pharmacol* 2018; 9: 1145.

167. France CP, Ahern GP, Averick S, *et al.* Countermeasures for preventing and treating opioid overdose. *Clin Pharmacol Ther* 2021; 109: 578–590.

168. Park EJ and Park YM. Opioid withdrawal and restless legs syndrome. *Chronobiol Med* 2020; 2: 137–140. DOI:https://doi.org/10.33069/cim.2020.0026.

169. Sharma S, Kumar P, Singh R, *et al.* Psychotic symptoms in heroin withdrawal: a case report. *Cureus* 2021; 13: e12620.

170. Kruszecki C, Cameron CR, Hume AL, *et al.* A systematic review of integrative medicine for opioid withdrawal. *J Subst Abuse Treat* 2021; 125: 108279.

171. Mojica MA, Carter MD, Isenberg SL, *et al.* Designing traceable opioid material § kits to improve laboratory testing during the US opioid overdose crisis. *Toxicol Lett* 2019; 317: 53–58.

172. Morrow JB, Ropero-Miller JD, Catlin ML, *et al.* The opioid epidemic: moving toward an integrated, holistic analytical response. *J Anal Toxicol* 2019; 43: 1–9.

173. Krasowski MD, McMillin GA, Melanson SEF, *et al.* Interpretation and utility of drug of abuse screening immunoassays: Insights from laboratory drug testing proficiency surveys. *Arch Pathol Lab Med* 2020; 144: 177–184.

174. Garneau B, Desharnais B, Beauchamp-Doré A, *et al.* Challenges related to three cases of fatal intoxication to multiple novel synthetic opioids. *J Anal Toxicol* 2020; 44: 86–91.

175. Dadiomov D. Laboratory testing for substance use disorders. In: Marienfeld C (ed.) *Absolute addiction psychiatry review*. Cham: Springer, 2020, pp. 17–30.

176. Truver MT and Swortwood MJ. Quantitative analysis of novel synthetic opioids, morphine and buprenorphine in oral fluid by LC-MS-MS. *J Anal Toxicol* 2018; 42: 554–561.

177. Pardo B, Davis LM and Moore M. Characterization of the synthetic opioid threat

profile to inform inspection and detection solutions. Homeland Security Operational Analysis Center (HSOAC), RAND CORP Santa Monica United States, 2019, https://www.rand.org/pubs/research_reports/RR2969.html

178. Moody MT, Diaz S, Shah P, *et al.* Analysis of fentanyl analogs and novel synthetic opioids in blood, serum/plasma, and urine in forensic casework. *Drug Test Anal* 2018; 10: 1358–1367.

179. Gilbert N, Antonides LH, Schofield CJ, *et al.* Hitting the jackpot – development of gas chromatography–mass spectrometry (GC–MS) and other rapid screening methods for the analysis of 18 fentanyl-derived synthetic opioids. *Drug Test Anal* 2020; 12: 798–811.

180. Al-Matrouk A, Alqallaf M, AlShemmeri A, *et al.* Identification of synthetic cannabinoids that were seized, consumed, or associated with deaths in Kuwait in 2018 using GC–MS and LC-MS-MS analysis. *Forensic Sci Int* 2019; 303: 109960.

181. Breindahl T, Kimergård A, Andreasen MF, *et al.* Identification of a new psychoactive substance in seized material: the synthetic opioid N-phenyl-N-[1-(2-phenethyl) piperidin-4-yl] prop-2-enamide (Acrylfentanyl). *Drug Test Anal* 2017; 9: 415–422.

182. Misailidi N, Athanaselis S, Nikolaou P, *et al.* A GC–MS method for the determination of furanylfentanyl and ocfentanil in whole blood with full validation. *Forensic Toxicol* 2019; 37: 238–244.

183. Fabresse N, Larabi IA, Stratton T, *et al.* Development of a sensitive untargeted liquid chromatography-high resolution mass spectrometry screening devoted to hair analysis through a shared MS2 spectra database: a step toward early detection of new psychoactive substances. *Drug Test Anal* 2019; 11: 697–708.

184. Richeval C, Gicquel T, Hugbart C, *et al.* In vitro characterization of NPS metabolites produced by human liver microsomes and the HepaRG cell line using liquid chromatography high resolution mass spectrometry (LC-HRMS) analysis: application to furanyl fentanyl. *Curr Pharm Biotechnol* 2017; 18: 806–814.

185. Hall AB, Coy SL, Nazarov E, *et al.* Development of rapid methodologies for the isolation and quantitation of drug metabolites by differential mobility spectrometry–mass spectrometry. *Int J Ion Mobil Spectr* 2012; 15: 151–156.