

Introduction: Fentanyl is available in many forms. *Pharmaceutical fentanyl* is used for managing acute or chronic pain, *illicit fentanyl* can be manufactured for use in the illegal drug market and in addition there are currently over 40 *fentanyl analogues* (see page 6) that vary in strength, effects and toxicity. For the purpose of this information sheet, the term *fentanyl*s will be used to cover all of these variations.

Background: Fentanyl is a powerful synthetic and short-acting painkiller that is 50-100 times more potent than morphine,¹ meaning that 1/10th of a gram of fentanyl is equivalent to between 5-10g of morphine*. It was first synthesized by Dr. Paul Janssen in December 1960^{2,3} and has become one of the world's most important and frequently used opioid analgesics, used also as a pre-medication for general anaesthetic, partly because of its rapid action and multiple routes of administration.

While pharmaceutical fentanyl can be diverted for misuse, cases of fentanyl-related mortality in the US have been linked to illicitly manufactured fentanyl and a variety of fentanyl analogues.⁴ These newly-synthesized fentanyl analogues are being sold as a standalone product, as a low-cost additive to increase the potency of heroin and even as counterfeit medicines.^{5,6,7} The overdose death rate from synthetic opioids (excluding methadone but including fentanyl and tramadol) continues to increase in the US with a 72.2% increase from 2014 to 2015, with a total of 9,580 deaths in 2015.⁸



Fig. 1: Pharmaceutical fentanyl (patches)



Fig. 2: Illicit fentanyl. Image: US Drug Enforcement Administration

UK & Irish context: The UK National Crime Agency (NCA) found that since December 2016, post mortem toxicology results indicate that 60 drug related deaths in the UK were known to be linked to fentanyl or one of its analogues.^{6,9}

The EU early warning system reported in July 2017 that exposure to carfentanyl had been analytically confirmed in 29 deaths in the UK, 28 of which occurred between February and May 2017.⁹

* Comparative strengths can be misleading: see page 7

There have also been an increasing number of reports from coroner's inquests around the UK & Ireland of fatal overdoses linked to fentanyls along with other drugs: from Cardiff,¹⁰ Stoke on Trent,^{11,12} Deal,¹³ Birmingham¹⁴ and Manchester.¹⁵

Heroin-related deaths in the North East have also shown positive results for fentanyl,¹⁶ and the Welsh Drug Identification Service WEDINOS have received 18 samples containing fentanyls since 2013.¹⁸



Fig. 3: Comparing the size of lethal doses of heroin, fentanyl, and carfentanil. The vials here contain an artificial sweetener for illustration. Image by kind permission of Bruce Taylor/ New Hampshire State Police Forensic Lab

In 2016 The Health Service Executive released an alert linked to deaths in Ireland¹⁹ and in April 2017 Public Health England (PHE) released an alert advising of evidence of heroin mixed with fentanyl or carfentanil in post-mortem results of recent drug deaths and from police seizures.²⁰ In addition, coroners from Swansea²¹ and South Tyneside and Gateshead²² have made public appeals to warn users about the dangers of fentanyl, amid concerns that users were not aware that they were taking the drug.

Despite international public health alerts,^{19,20,23,24} research²⁵ and multiple media reports about heroin, cocaine and even MDMA^{26,27,66} users inadvertently buying drugs adulterated with fentanyl, it is unclear how widespread this is in the UK at the current time. The NCA report from April 2017 which found fentanyl in heroin tested from street seizures in the Yorkshire area¹⁷ has been widely referenced, and samples from WEDINOS have contained fentanyls where users had intended to buy heroin or other drugs.¹⁸ However the extent to which fentanyl has been added to illicit drugs without users' knowledge as opposed to being purchased intentionally (e.g. from the dark web) remains unknown.

A representative from a company which tests biological samples for coroners for pathology labs reported that carfentanil or fentanyl had been found in up to 46 cases in the UK since March 2017, adding that about three or four of the 15 cases

received every week were testing positive for the substances but that in most instances a coroner had not yet recorded an official cause of death.²⁸ Reports from both the UK and US find that the true number of overdoses linked to illicitly manufactured synthetic opioids is most likely higher because these drugs may not show up in standard toxicology results and many toxicologists do not test for the drugs unless given a specific reason to do so.^{16,29,30,31}

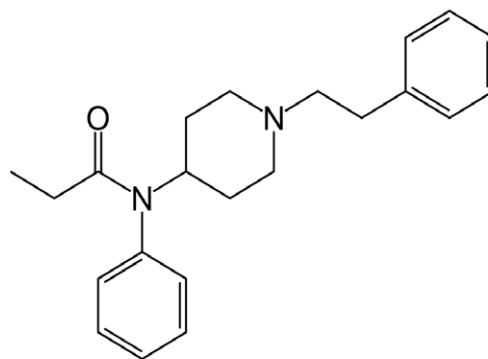


Fig. 4: Fentanyl molecule

Drug class: The fentanyls are fast-acting, potent synthetic mu receptor-stimulating opioid analgesics.³² Their method of action is believed to involve the binding to the transmembrane mu-opioid receptors on cell surfaces resulting in a cascade of intracellular signals that eventually results in their biological effect,^{33,34} however to date a detailed description of this receptor binding event remains undiscovered.³⁵

Routes of administration: Pharmaceutical fentanyl products are currently available in the following forms: oral lozenges commonly referred to as fentanyl “lollipops”, effervescent buccal tablets (held in the cheek to dissolve in the tissues of the mouth), sublingual tablets, sublingual sprays, nasal sprays, transdermal patches, and injectable formulations.



Fig. 5: Fentanyl 'lollipops'

Fentanyl can be extracted from its transdermal (patch) form by removing its gel contents and then injecting or ingesting these contents. Patches have also been frozen, cut into pieces and placed under the tongue or in the cheek cavity. All routes of administration have been reported including: nasal insufflation (sniffing), sublingual nasal spray, rectal and intravenous injection,^{36,37} inhalation via burning powder on aluminium foil, inhalation via a vaporizer and oral (including being sold online in blotter form). Another concern is the appearance on the market of nasal sprays containing fentanyl analogues such as acryloylfentanyl and furanylfentanyl.⁷

Legal status: Fentanyl and its analogues are classified as Class A Controlled Drugs under the Misuse of Drugs Act 1971. A number of its precursors are currently not controlled under the Misuse of Drugs Act, however are probably[†] controlled under the Psychoactive Substances Act.

Appearance and taste: Fentanyl is a white powder when pure, having been referred to by users as 'China White' or 'white heroin'. There are conflicting user reports as to its appearance when mixed with heroin: some users report that it has a grey, silvery appearance when cooked and drawn into a needle, however others claim that there is no difference and that it is impossible to tell when heroin has been cut with fentanyl.³⁸

Onset, duration of effects and half-life: Analgesia may occur as soon as 1 to 2 minutes after intravenous administration of fentanyl, whereas most buccal transmucosal delivery systems produce analgesia in 10 to 15 minutes.³⁹ In contrast, sublingual and intranasal sprays of fentanyl may produce analgesia in 5 to 10 minutes or sooner.⁴⁰ Fentanyl plasma concentrations do not peak or plateau until 8 to 16 hours after application of a transdermal patch.⁴¹



Fig. 6: Ampoule of pharmaceutical fentanyl citrate



Fig. 7: Fentanyl nasal spray

Predicting duration of effect and half-life of fentanyl is a complex issue, affected by a number of factors. Its duration of action usually lasts 2 to 4 hours after intravenous or transmucosal delivery, but blood levels fall quite slowly after transdermal patch removal. The half-life of fentanyl varies significantly: ranging from 3-12 hours following injection (IV or IM) with fentanyl citrate,^{42,43} which increases to approximately 17 hours when administered by transdermal system. This variation is due to continued absorption of fentanyl from the skin accounting for a slower disappearance of the drug from the blood.^{2,43} It is of note that some fentanyl analogues such as alfentanil have a significantly shorter half-life.⁴⁴

[†] Nothing is controlled under the Psychoactive Substances Act until it has gone before a court that has concluded that it is psychoactive.

Testing: Fentanyl does not show up in many standard urine tests. The appropriate testing technology is high resolution mass spectrometry, the main benefits of which are sensitivity, universal application and the ability to detect new compounds retrospectively (without the need to repeat the analysis). Fentanyl testing strips are also available,⁴⁵ however these currently do not differentiate between fentanyl and its analogues and may not detect the more potent illicit fentanyl compounds.

Dosage information: The recreational use of products containing fentanyl may easily prove fatal. This can be due to administered dose, a change in dose or a change in the route of administration (e.g. extracting the drug from a transdermal patch into liquid to prepare an injection or nasal spray, inhaling volatilised fentanyl or inhalation of dust, or placing a transdermal patch on oral mucous membranes). Attempts to prepare a single dose by weighing without precision equipment are highly risky, and illicitly manufactured fentanyl amplifies the hazards because such products lack quality control, are typically not portioned in precise doses and can be deadly in minuscule amounts due to their extreme potency.⁴⁶ Tolerance is a critical issue for users of fentanyl: it acts additively with other opioids and depressants and with prolonged use tolerance may be developed.⁴⁷ Due to the difficulty of predicting duration of effect, half-life and the wide variation in strength and effect of the fentanyl it is not possible to discuss non-medical dosage information.

Drug effects:

| Physical | Mental |
|---|--|
| <p>Analgesia, drowsiness, disorientation, clammy skin, fatigue, sedation, nausea, vomiting, respiratory depression (leading to apnea in higher doses), suppression of cough reflex, constriction of pupils (miosis), impaired gastrointestinal motility, dizziness, slow heart rate (bradycardia, secondary to a central vagal stimulating action) and unconsciousness/anesthesia in higher doses irrespective of the mode of administration.^{48,49}</p> <p>Some users have described physical effects of “tingling” or “pins and needles”.³⁸</p> | <p>Alteration in mood, euphoria, relaxation, sense of invincibility, floating feeling, dreamlike state and visual hallucinations.</p> <p>In rare cases, symptoms of delirium have also been noted, including: confusion, restlessness, agitation and paranoia.^{50,51}</p> |

Analogues: In chemistry, an analogue is defined as *a compound with a molecular structure closely similar to that of another*.⁵² Since the original synthesis of fentanyl, analogues with superior strength, onset time and other properties have been successfully produced.⁴⁷ Analogues of fentanyl can vary depending on the chemical structure, with some being less potent/toxic than fentanyl and some being significantly more. There has been documented military misuse of these analogues for their crowd controlling properties: in a particularly infamous case the presumed use of gaseous/aerosolized fentanyl derivatives by Russian security forces to incapacitate terrorists during a Moscow theatre hostage crisis in 2002 led to the death of over 100 people, including hostages, through a combination of the aerosol and inadequate medical care.⁵³



Fig. 8: Packaged fentanyl seized in Calgary, Alberta. Image by kind permission of Calgary Police Service.

In the opioid overdose cases in the US in 2015, fentanyl analogues were implicated in 17% of cases where the presence of these drugs was examined.³⁰ The powerful effects of these compounds at such low doses combined with the lack of medical training in cases of illicit use make these drugs extremely dangerous outside the clinical environment. To reduce the potency of fentanyls to usable levels they need to be bulked out with filler agents, and it is very difficult to mix a few micrograms of a drug such as carfentanil thoroughly into a bulk powder such as heroin to get an evenly-mixed, homogeneous product. In addition, because of the wide range and variety of fentanyl analogues there is a chance of misidentification or mis-selling throughout the supply chain.⁵⁴

Overall, 18 new fentanyl analogues have been detected in Europe's drug market since 2009, eight of which were reported for the first time in 2016.⁷ There are currently more than 40 fentanyl analogues, the four below are some of the more commonly-seen at the time of this document being created:

| | |
|------------------|---|
| Acetylfentanyl | Acetylfentanyl was subject to an EMCDDA-Europol joint report in 2015 after being associated with 32 deaths, two of which were in the UK. ^{55,65} Studies suggest that it is 15 times more potent than morphine. ^{26,56} |
| Acryloylfentanyl | The synthesis of acryloylfentanyl was first described in 1981. ⁶⁷ Countries that reported its use to the EMCDDA informed Europol that it was ordered in powdered form from China, mainly purchased through the internet and then used either in powder form or to make tablets, capsules and solutions for injection and nasal sprays. ⁶⁸ |
| Carfentanil | Carfentanil was previously used exclusively for veterinary use with large animals but has also been described as a chemical warfare agent. It is not approved for use in humans and (along with other fentanyl analogues) presents a serious risk to public safety, first responder, medical, treatment and laboratory personnel as it can be absorbed through the skin or accidentally inhaled. It can be lethal at the 2-microgram range (approximately 1/50th the size of a grain of sugar), ⁵⁷ depending on route of administration and other factors. |
| Ocfentanil | Ocfentanil was first detected in Europe in September 2013 and since then it has been detected in a total of 11 countries. Ocfentanil has been detected in samples purchased as heroin on the dark web and has been otherwise sold as <i>black tar</i> or <i>synthetic heroin</i> . Ocfentanil has also been found in mixtures containing heroin and is 125-250 times more potent than morphine. ⁵⁸ As of June 2016, the EMCDDA has received reports of two deaths and three non-fatal intoxications associated with ocfentanil. ⁵⁵ |

Comparative strengths: While it is often helpful to discuss comparative strengths of drugs these comparisons are not always what they seem. Variables such as speed of onset, duration of effect and level of analgesia as opposed to sedation play a significant part in a drug's strength of effect.⁵⁴

Harm reduction: Issuing warnings about ‘dangerous’ or ‘high-strength’ fentanyl can be counterproductive. On the one hand, they raise awareness and highlight the dangers; on the other they risk publicising a high strength, low-cost alternative to street heroin and can make it a sought-after product. Fentanyl is not currently widespread and services are encouraged to develop locally relevant messages that do not inadvertently promote them.⁵⁴

For users:

- **Don’t inject alone.** Use with people who can respond in the event of an emergency; if using together don’t all use at the same time.
- **Make sure you have naloxone** and a phone that works.
- Fatal overdose is possible from smoking fentanyl, however smoking puts you at a lower overdose risk than injecting.
- If injecting, sampling batches before use and injecting slowly can reduce risk.
- Mixing drugs increases the risk of overdose, especially when opioids are used with alcohol or other sedating drugs like Valium, Zopiclone, gabapentin or pregabalin.
- Fentanyl overdoses can reportedly be very rapid. Watch carefully for signs of an overdose (e.g. loss of consciousness, shallow or absent breathing, ‘snoring’ and blue or paler lips or fingertips).
- If you do not have naloxone and someone overdoses, call an ambulance, put them in the recovery position and if possible stay with them until help arrives. If they are not breathing normally and you know First Aid, CPR is required to give extra oxygen via rescue breaths.

For drug treatment services:

- Warn services users, and where possible others not in contact with services about the risks of heroin cut with fentanyl.
- Supply naloxone so that it is available for all those at risk. PHE and HSE⁵⁹ recommend using standard naloxone dosing regimes.
- While IV use remains the most high risk route of administration there are numerous reports of fatal overdose from pharmaceutical-grade fentanyl patches^{60,61,62} and it is important to emphasize the potential risk of fatal overdose from smoking and other routes of administration.

- Provide rapid access to treatment, including substitute opioids, for heroin users.
- Engage with service users to find out what drugs are on the market, and if 'white heroin' or other products potentially laced with fentanyls are appearing locally.
- Be aware that some medicines (including SSRIs and methadone) can interact with fentanyl and cause serotonin syndrome.^{63,64}

For local authority and health commissioners:²⁰

- Take steps to ensure that harm reduction information about fentanyls is made available to heroin users who are not in contact with drug treatment services.
- Make efforts to ensure that other relevant services, e.g. homelessness hostels are also aware of the current risk.
- Make bulletins up to date and locally relevant.
- Ensure that facts are established before cascading information by developing a local drugs warning protocol in conjunction with user groups, police and public health.

For First Aiders:

While all use of street opiates brings a risk of overdose, the potency and variability of fentanyls bring an unparalleled level of risk.

- Be aware of any sign of exposure. Symptoms include: respiratory depression or arrest, drowsiness, disorientation, sedation, pinpoint pupils and clammy skin. The onset of these symptoms usually occurs within minutes of exposure. Seek immediate medical attention: fentanyls can work very quickly so in cases of suspected exposure call 999 immediately.
- Be ready to administer naloxone in the event of exposure. Naloxone is an antidote for opioid overdose, and immediately administering it can reverse an overdose of opioids. Continue to administer a dose of naloxone every 2-3 minutes until the individual is breathing on his/her own and is responsive to verbal and physical stimulus (being spoken to and having their cheek or elbow touched or gently shaken) for at least 15 minutes or until told to discontinue by ambulance or paramedic staff on the scene of the incident.

For Emergency departments and Paramedics:²⁰

The standard naloxone dosing regime where overdose from fentanyl is suspected (for adults and children >12 years) for use in acute hospitals, subject to clinical assessment of the individual case, is:

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

For all First Responders:

The high potency of analogues such as carfentanil in particular is of concern and First Responders should exercise caution. Lethal overdose can be caused by the ingestion of minute quantities of some fentanyl analogues; this includes being absorbed via the skin and through an intake of breath.^{16,60,70,71,72} If you suspect the presence of any synthetic opioid, do not take samples or otherwise disturb the substance as this could lead to accidental exposure.

Recovery Position:

The recovery position is for someone who is unconscious but breathing normally. If they are not breathing normally CPR is required, with an emphasis on giving supplementary oxygen via rescue breaths.



Start by placing their arm as if they are waving.



Place the other arm across their chest and hold their hand against their cheek.



Lift up the knee that is furthest from you. Continue to hold their hand in place.



Turn them on their side by pulling the knee towards you and down.

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For further information on Overdose & Emergencies see [UK and Ireland DrugWatch Information Sheet](#).

Where to get help: We would advise anyone experiencing issues from fentanyl or other substances to seek medical support via their GP or the NHS. There are a wide range of local drug services throughout the UK, to find out what is available in your area please use the links below:

England: [Find Support | Frank](#) Scotland: [Scottish Drug Services](#)
Wales: [Dan 24/7](#) Northern Ireland: [Public Health Agency](#) ROI: [Drugs.IE](#)

For further advice, medical professionals can use the National Poisons Information Service 24-hour telephone service on 0344 892 0111 or its online database, TOXBASE. Any health professional encountering an unusual or unexpected adverse reaction to the use of heroin (or any other drug) should report the reaction to [RIDR](#).

Written by [Mark Adley](#) in association with [UK and Ireland DrugWatch](#): an informal online professional information network established by a group of professionals working in the UK and Irish drugs sector. The aim of the group is to raise/establish standards for drug information, alerts and warnings. It is currently an unfunded, bottom-up initiative that works in the spirit of mutual co-operation. Details of current members can be found [here](#).

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Images

Fig.1 Fentanyl patch packages from several German generic drug manufacturers (from left to right: 1A Pharma, Winthrop, TAD Pharma, Ratiopharm, Hexal). By Alcibiades (Own work) [Public domain], via Wikimedia Commons from Wikimedia Commons https://commons.wikimedia.org/wiki/File%3AFentanyl_patch_packages.jpg [Accessed July 2017].

Fig.2 Fentanyl in powder form. DEA Press Room <https://www.dea.gov/pr/multimedia-library/image-gallery/fentanyl/Fentanyl%20in%20powder%20form.jpg> [Accessed July 2017].

Fig.3 Comparing the size of lethal doses of heroin, fentanyl, and carfentanil. By kind permission of Bruce Taylor/New Hampshire State Police Forensic Lab. [Permission given by email on 25/07/2017].

Fig.4 Fentanyl molecule. By Harbin (Own work) [Public domain], via Wikimedia Commons from Wikimedia Commons <https://commons.wikimedia.org/wiki/File%3AFentanyl.svg> [Accessed July 2017].

Fig.5 Fentanyl Lozenges. http://www.opiateaddictionresource.com/media/images/fentanyl_lozenges [Accessed July 2017].

Fig.6 Ampoule of pharmaceutical fentanyl citrate. http://www.opiateaddictionresource.com/media/images/fentanyl_iv [Accessed July 2017].

Fig.7 Fentanyl nasal spray. By BQT QT (Own work) [CC BY-SA 4.0 (<http://creativecommons.org/licenses/by-sa/4.0/>)], via Wikimedia Commons from Wikimedia Commons https://commons.wikimedia.org/wiki/File%3APecFent_bottle.JPG [Accessed July 2017].

Fig.8 Packaged fentanyl seized in Calgary, Alberta. Image by kind permission of Calgary Police Service. [Permission given by email on 25/07/2017].