FEBRUARY 2024

# Naloxone: Legal Challenges and Opportunities for Life Saving Intervention

ALEXANDRE PIOT

Centre for Evidence Based Drug Policy

# Foreword

With drug-related deaths at an all-time high, mainly driven by opioid use, it is far beyond time that the government take steps to push UK drug policy in the right direction. That is why I'm proud to endorse the call of the Centre for Evidence Based Policy to expand access to naloxone further.

Naloxone, a powerful antidote, swiftly reverses the life-threatening consequences of an opioid overdose, restoring breathing within minutes. I have personally witnessed this remarkable effect at a homeless shelter, where a man on the brink of an opioid overdose had his life saved by a timely administration of naloxone.

Increasingly potent synthetic opioids are making their way into our country and communities, resulting in incalculable losses for families and loved ones of those who have passed. While the full complexity of the solutions matches that of the problem, the overall ask is clear: to govern drug policy from a health-centred perspective and put an end to the senseless war on drugs and the people who use them. More than fifty years after the Misuse of Drugs Act was first enacted, it is clear that this approach is not working.

Expanding access to naloxone, a life-saving medication, is a positive step in the right direction and an evidence-based policy with the potential to save lives and reverse the ever-increasing number of drug-related deaths. Other jurisdictions have already taken steps to provide naloxone prescription-free, and while the His Majesty's Government made significant advancements in 2015, it is time for even further expanded access.

*Adam Holloway MP, Co-chairman of the Centre for Evidence Based Drug Policy*

# Executive Summary

Emerging reports indicate that the UK's illicit opioid supply is increasingly being contaminated with highly potent synthetic opioids such as fentanyl and nitazenes which have been linked to clusters of overdoses. Naloxone is a life-saving medication, administered to reverse an opioid overdose.

The benefits of naloxone administration strongly outweigh the risks, it is used to treat a readily identifiable condition, it has no potential for misuse and its administration is straightforward and safe following a brief training. While the 2015 changes made to the Human Medicines Regulation 2012 allowing the distribution of naloxone by drug treatment services to save lives in an emergency are welcome, they fail to capture essential pockets of the population who do not engage with drug treatment services such as family, friends and members of the public who come into contact with people who use drugs. Moreover, the prescription-only classification of naloxone hinders the broadening of public awareness regarding its life-saving attributes through public promotional/educational campaigns.

Over-the-counter naloxone is already being provided in jurisdictions facing the threat of synthetic opioids such as Canada and the United States. In this report, we strongly recommend the reclassification of naloxone hydrochloride as a Pharmacy (P) medication. This strategic move aims to significantly decrease the incidence of drug-related deaths across the UK and counteract the surge in highly potent synthetic opioids, aligning with the objectives outlined in the Government's 10-year drug strategy.

Alternatively, should reclassification prove challenging, we propose enhancements to the Department of Health and Social Care's proposed legislation. These suggested improvements are designed to optimise the accessibility of naloxone and enhance public awareness regarding its availability.

# What are synthetic opioids?

*North America has witnessed a significant increase in the proportion of synthetic opioids such as fentanyl, its derivatives, and nitazenes, which have significantly worsened the ongoing opioid epidemic [1]. A similar increase in the UK is expected over the coming months, the beginning of which has already appeared. Due to their greater potency compared to typical opioids like heroin and morphine, synthetic opioids are easier to smuggle, significantly heighten the risk of fatal overdose, and necessitate larger doses of naloxone for effective overdose reversal [2–4]. As a response to this, the United States Food and Drug Administration has licensed several formulations of naloxone for over-the-counter sale [5].*

## Nitazenes

Nitazenes are a collection of synthetic opioids developed in the 1950s but were never approved for human use in the UK. Their potency ranges from 1 to 1000 times more potent than morphine [6]. To illustrate this, a dose of isotonitazene would cause the same physiological effects as a dose of morphine 500 times larger (10mg of nitazene would equate to 5000 mg of morphine). While the lethal dose of nitazenes in humans is not yet known, the potency of these compounds suggests that less than 10 mg is enough to induce an overdose, 95% less than the typical daily dose of heroin administered intravenously for the management of heroin dependence in clinical contexts [7,8].

## Fentanyl and derivatives

Fentanyl is 50-100 times stronger than morphine [9–11]. Counterfeit pills containing as little as 5.63 mg of fentanyl (1.34% of the total pill weight) have been shown to induce overdoses [12]. The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) estimates that the lethal dose of fentanyl is only 2mg [13] (the same weight as 10-15 grains of salt). Carfentanil, a fentanyl derivative, is estimated to be 20 times stronger than fentanyl [14] (100-200 times more potent than morphine). One kilogram of carfentanil is enough to cause 20 million fatal overdoses [14]. That is more than twice the population of London.

Reports of carfentanil deaths have already emerged in the UK [15,16]. There were 22 seizures of fentanyl and its analogues in England and Wales in the year ending in March 2022, and 35 the previous year [17].

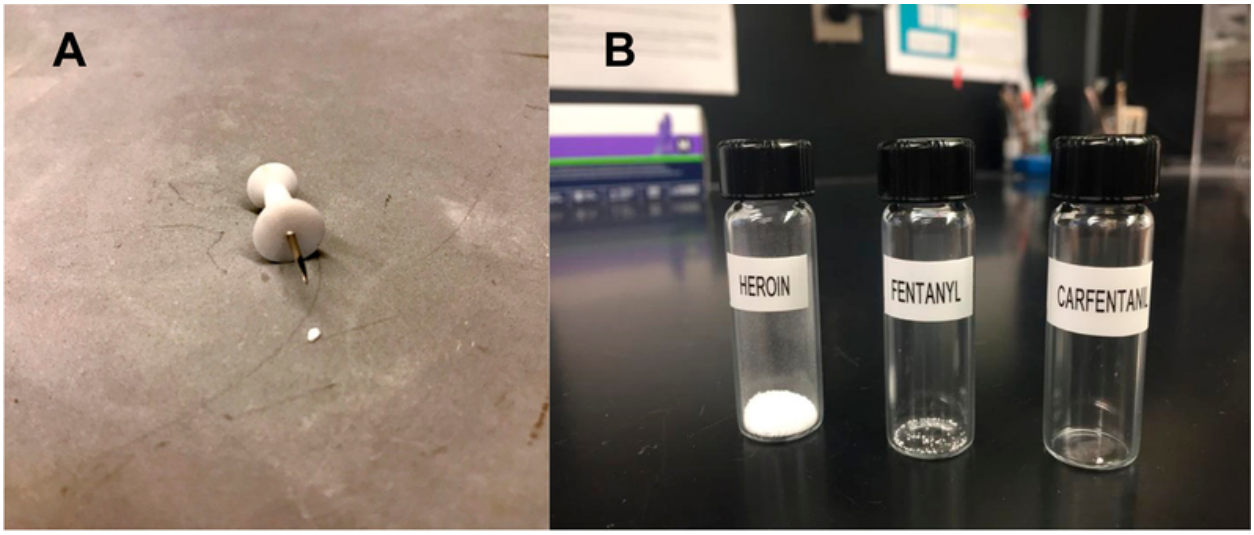


Figure 1. (A) Size of 1mg of powder. (B) Size comparison of lethal doses of heroin, fentanyl and carfentanil. *Source: Ringuette, Anna E., Matthew Spock, Craig W. Lindsley, and Aaron M. Bender. "DARK classics in chemical neuroscience: carfentanil." ACS Chemical Neuroscience 11, no. 23 (2020): 3955-3967. https://doi.org/10.1021/acschemneuro.0c00441; Photo by Paige Sutherland for New Hampshire Public Radio.*

# The rise of opioids overdose deaths in the UK

*While the UK seems to have so far been spared a rise in the use of synthetic opioids, the tide appears to be turning. Nitazenes were first detected by the drug testing service WEDINOS (Welsh Emerging Drugs and Identification of Novel Substances) in July 2021. From April 2022 to March 2023, 36 samples were identified by WEDINOS as containing nitazenes. In July 2023 a National Patient Safety Alert was sent by the Office for Health Improvement and Disparity to flag the elevated number of overdoses involving nitazenes found in heroin and counterfeit pharmaceutical tablets sold as benzodiazepines [18]. In June-July 2023 16 people died in Birmingham, and the latest data indicates that since June 2023, 54 deaths have been linked to nitazenes in the UK (Table 1). This number is likely an underestimate given that post-mortem testing for nitazene when investigating apparent drug-related deaths is not standard in the UK [19].*

While the UK's very limited national drug testing capabilities make it difficult to know the full scale of the problem, the EMCDDA has noted a notable increase in the prevalence of synthetic opioids and related deaths in the last few years [20]. For example in Ireland, 40 deadly overdoses were reported to the Irish Health Service Executive in 36 hours in November 2023 [21]. Similar clusters of overdoses have been noted in Belfast [22] and Birmingham [23].

| Region | Number of Deaths (June 1st-December 7th 2023) |
|---|---|
| West Midlands | 17 |
| East of England | 9 |
| Scotland | 9 |
| South East England | 6 |
| South West England | 5 |
| Yorkshire & Humber | 3 |
| East Midlands | 2 |
| London | 2 |
| North West England | 1 |
| Total | 54 |

Source: National Crime Agency and BBC

Table 1. Over approximately 6 months, 54 deaths were reported as linked to nitazenes. These numbers are likely underreported as testing for nitazenes in not yet standard practice in post mortem toxicology tests.

The increased prevalence of synthetic opioids coincides with the ban on opium cultivation instated by the Taliban in April 2022 [24]. In 2000 and 2001 the Taliban enforced a similar nationwide ban on the production of opium poppy which did not result in major disruptions to the opiate market [25]. This is believed to be due to the short-lived nature of the ban and the sufficient supply of heroin at other points in the supply chain to sustain demand [25]. However with the increased availability of synthetic opioid precursors online, and the ease of smuggling fentanyl, this gap in the market is expected to be rapidly filled with the next generation of synthetic opioids.

HMG has recently taken steps to classify nitazenes as Class A substances [26] following advice from the Advisory Council on the Misuse of Drugs (ACMD), but there is currently no evidence of the deterrent effects of stricter classification reducing drug use [27–30]. Furthermore, heroin and other opioids have been Class A for decades and overdose rates continue to increase (Figure 2). It is also of note that several of the ACMD's key recommendations were not directly accepted by the Home Office, further stifling the UK's ability to respond to and manage this impending crisis [26].

**One of the most straightforward and cost-effective measures His Majesty's Government can take to reverse this trend is to ensure the antidote for opioid overdose is accessible and that citizens and professionals are educated on how and when to use it.**

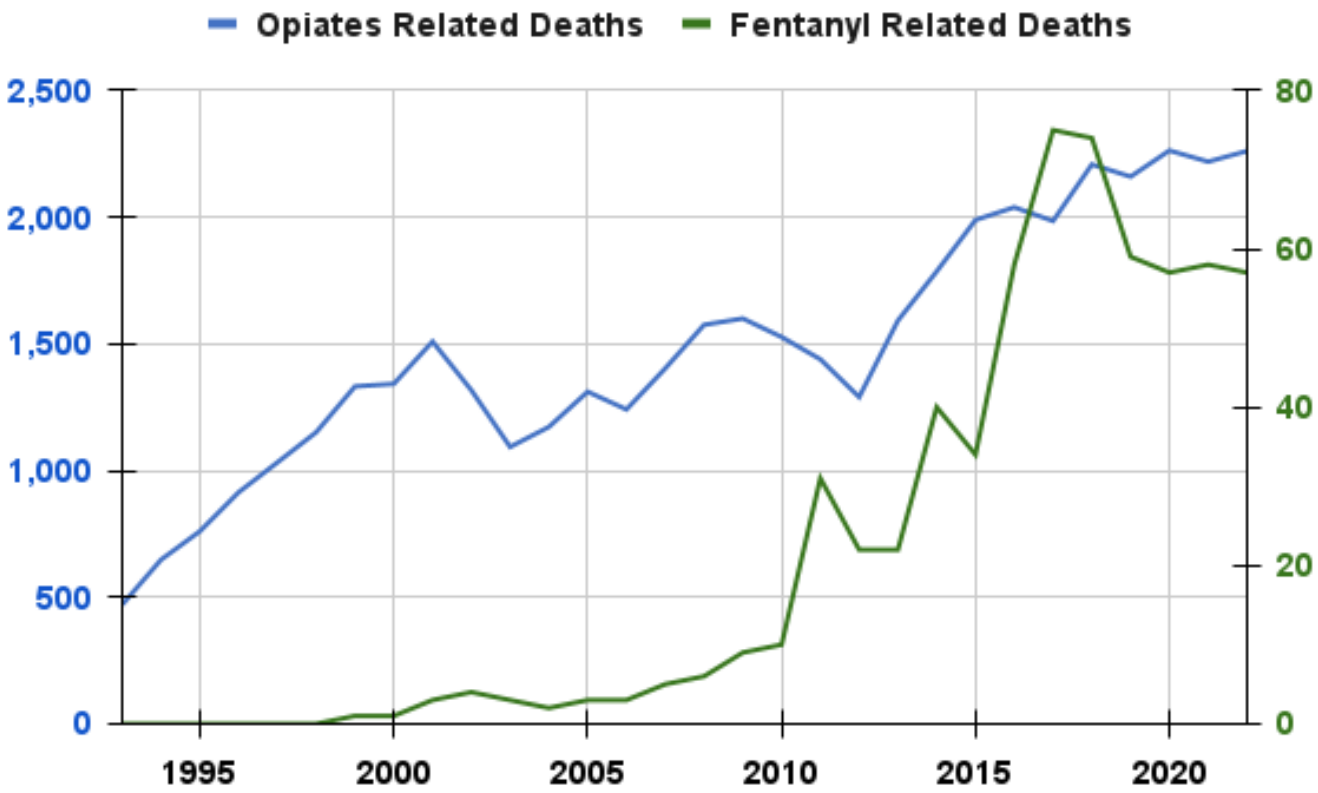


Figure 2. Opiate and Fentanyl related deaths in England and Wales from 1993-2022. An 82% increase in fentanyl related deaths in the last 10 years. No official data on the number of nitazene deaths have yet been published, but government responses to Written Parliamentary Questions (WPQs) reveal that the number of nitazene deaths in the UK is estimated at 64. *Source: https://www.ons.gov.uk/ ; WPQ UIN 11885*

# How does Naloxone work?

*Naloxone is an μ-opioid receptor antagonist which competitively binds with strong affinity to the same receptor site as opioids [31], thereby displacing the compound inducing the overdose from the receptor and reversing the symptoms of overdose. When administered in the absence of opioids, naloxone shows negligible side effects [32]. The pharmacological action of naloxone is inverse to that of opioids and it is not liable to recreational use or abuse, producing no subjective effects or dependence [33].*

## Pharmacodynamics

While naloxone binds to most opioid receptors, its overdose reversal effects are exerted at the μ-opioid receptor. The ability of naloxone to reverse an overdose is dependent on the binding affinity of the opioid binding to the μ receptor. Opioids which bind more strongly with the μ-opioid receptor are more difficult to dissociate from the receptor with naloxone.

## Pharmacokinetics

Naloxone is not bioavailable following first-pass metabolism and therefore cannot be administered orally [34]. The bioavailability of naloxone is also low sublingually (10-28%) and intranasally (4-30%) [31]. Intranasal bioavailability can also be further altered by factors such as the surface area, thickness, vascularity and clearance rate of the nasal mucosa, spray technique, and inter-individual differences in nasal anatomy and physiology [35]. Injectable naloxone, administered intramuscularly, intravenously, or subcutaneously, offers the highest bioavailability of naloxone for effective intervention. Several elements can influence the absorption of an injectable substance. Even though it's typically believed that injections deliver 100% of the dose, the actual absorption rates for intramuscular (IM) or subcutaneous injections can differ. This variation is dependent on factors such as the blood flow to and from the injection site, as well as the quantity of muscle and fat tissue present [35,36].

In non-medical settings, intramuscular injections are often favoured due to their easy accessibility and quick absorption rates compared to other parenteral methods; however, the intranasal version is preferred by some individuals to avoid the use of needles. One study found that the bioavailability of intranasal naloxone was only 47-51% that of intramuscular naloxone [36,37] therefore achieving equivalent plasma concentrations requires twice the amount of naloxone through the intranasal route. This can slow the response to an overdose, increase the associated cost and limit the chance that enough naloxone is rapidly available in an emergency. The scientific literature indicates that the effectiveness of intramuscular naloxone injections surpasses that of intranasal administrations for promptly reversing acute overdoses [38].

While the efficacy of a dose of naloxone is dependent on the pharmacological properties of the opioid causing the overdose, studies have indicated that the onset time for an effective dose of naloxone is similar for intranasal and intramuscular naloxone [36] however intramuscular naloxone injections are less likely to require a follow-up dose than intranasal administration [38–41].

A recent meta-analysis compared the efficacy of intranasal vs intramuscular naloxone in the prehospital management of opioid overdose [40]. While the success rates of intramuscular and nasal naloxone were equivalent (~80%) the onset of intranasal administration was longer and the need to administer a rescue dose was 2.17 times greater for intranasal naloxone [40].

## Side Effects of Naloxone

The most prominent side effect from the administration of naloxone is the precipitation of acute opioid withdrawal syndrome in persons addicted to opioids, which while uncomfortable, is non-lethal and a consequence of the drug being displaced from the receptors. Symptoms include nausea, vomiting, diarrhoea, anxiety and aggression. In rare cases, naloxone can precipitate noncardiogenic pulmonary oedema (0.2-3.6%) characterised by pink frothy sputum and occurring within 4 hours of naloxone administration [42].

## Safety of Naloxone

Naloxone is widely considered to be a safe and effective drug which can be administered in large doses with a good safety profile [43]. The side effects mentioned above are applicable to patients with an opioid dependence and are not life-threatening [31]. Several separate studies evaluating the outcome of pre-hospital naloxone administration in patients who refused further care observed no emergence of life-threatening events or deaths [44–46]. One study observed a single patient death (out of 205 cases) within 24 hours post naloxone administration due to heroin use and coronary artery disease [47]. Another risk associated with the administration of naloxone is that it may wear off before the opioid causing the patient to relapse into overdose. This information is communicated in leaflets distributed with naloxone kits and during training sessions to mitigate risks.

## Cost Effectiveness of Naloxone

Several studies conducted in the UK have demonstrated that distribution of naloxone is a cost effective measure for decreasing overdose related deaths. One study modelling the impact of take home naloxone in a limited population of heroin users indicated that providing take home naloxone to only 30% of heroin users could avert 6.6% of overdose fatalities [48]. This approach was also found to be cost-effective at an average of £156 per person [48]. This cost could range from £33 to £365 per person, depending on various factors [48]. The National Naloxone Programme initiated in Scotland in 2011 has been linked to a decrease of 36% in opioid-related deaths occurring within four weeks after individuals are released from prison [49]. Naloxone was found to be generally cost-effective in preventing post-prison release opioid deaths, its overall cost-effectiveness depends on various factors including QALYs gained, additional costs for training and outreach, and potential savings in healthcare and criminal justice expenses [49].

Research from abroad, mainly the United States currently facing an opioid crisis, has also thoroughly demonstrated the cost effectiveness of increased naloxone distribution. An evaluation of the distribution of naloxone to different groups such as lay people likely to witness or experience an overdose, police officers and firefighters, and emergency medical personnel, or a combination of these groups found that all

elevaluated strategies were cost effective with cost savings greatest in maximum distribution strategies [50]. **Expanding the distribution of naloxone to both the general public and first responder groups maximised the health benefits and proved to be economically efficient** [50]. Other research has consistently shown the cost effectiveness of increased naloxone distribution by leading to fewer overdoses or emergency medical service activations [51,52].

## Naloxone availability in the UK

Naloxone (in both its injectable and intranasal formulations) is currently a prescription only medication in the UK. Despite this, it is legal for anyone to administer naloxone to a person in order to save their life in an emergency [53]. A 2015 amendment to the Human Medicines Regulation allowed naloxone to be supplied without a prescription by drug and alcohol treatment services when commissioned by a named public body. Furthermore, a Patient Group Direction (PGD) allows certain healthcare professionals (like nurses or paramedics) to supply or administer naloxone to patients in specific situations [53]. It needs approval from a relevant authority, such as a health agency or NHS trust.

| Intranasal Formultation | Intramuscular Formulation |
|---|---|
| Is less invasive<br>Some people feel more comfortable adminsitering this formulation | Less likely to require a supplementary dose<br>Higher bioavailability and rapid absoprtion<br>Less expensive than an equivalent dose of intranasal formulation<br>More efficacious in reversing synthetic opioid overdoses |

Table 2. The most common formulations of naloxone available in the UK are Nyxoid (intranasal) and Prenoxad (intramuscular).

At the end of January 2024, His Majesty's government announced an open consultation on a proposal to further increase the availability of naloxone [54]. This consultation is being led by the Department of Health and Social Care, the Department of Health (Northern Ireland), the Welsh Government, and the Scottish Government. The proposed legislation would facilitate access to naloxone by:

- Amending Named Services and Professionals: Expanding the list of named services and professionals authorised to supply naloxone without a prescription.
- Implementing a Registration Route: Establishing a registration route that allows additional services and organisations to supply naloxone subject to training and safeguards.
- Ensuring Training and Support: Mandating appropriate training for all services and professionals involved in supplying naloxone.
- Enhancing Data Collection and Reporting: Introducing specific data reporting requirements to monitor naloxone supply effectively.
- Streamlining Supply Routes: Facilitating varied supply routes across the UK, tailored to the needs of different regions and services.
- Establishing a Naloxone Supply Network Coordinator: Designating a coordinator to manage the registration and distribution of naloxone supplies.

# Limitations of the Proposed Legislation

*The government has made commendable strides in enhancing access to naloxone, a critical step in addressing the challenges posed by opioid-related emergencies. The ongoing consultation and continued efforts to improve the availability and distribution of this life-saving medication are both welcome reflecting a proactive approach to public health and safety and refinement of the approach.*

## Challenges in Naloxone Access and Distribution

While the proposed legislation seeks to improve naloxone access, further refinement and clarification are essential to guarantee its effective and equitable distribution throughout the UK. Notably, the inconsistency in defining certain services like temporary or supported accommodation and outreach and day services across the UK Government and devolved administrations raises concerns of uneven naloxone access and distribution. The proposed scheme addresses this by allowing services not named in the legislation to register for naloxone supply. However, as the legislation does not mandate the supply of naloxone by named services and professionals, it risks uneven availability across regions and services.

## Towards a Comprehensive Framework for Naloxone Distribution

Moreover, mandating key professions like police officers or emergency medical services to carry naloxone could be crucial. The implementation of safeguards and governance, especially under the registration route, presents potential challenges in consistency and execution across services and regions. Additionally, the temporary measures introduced in Scotland during the COVID-19 pandemic highlight the need for a permanent, comprehensive framework for naloxone distribution. **The current prescription-only status of naloxone limits vital public education on its life-saving properties. Therefore, short of reclassifying naloxone from a Prescription Only Medicine (POM) to a Pharmacy (P) medication, exceptions to facilitate publicity and educational campaigns about naloxone use, especially in areas with higher opioid use, should be considered.**

It is worth noting that the proposed amendment is only a draft and these points may be addressed in further drafts following the public consultation which is closing on March 6th 2024. Link to the consultation:

https://www.gov.uk/government/consultations/proposals-to-expand-access-to-take-home-naloxone-supplies/proposals-to-expand-access-to-take-home-naloxone-supplies

Crucially, it is important to address problems associated with heroin overdose upstream by increasing the implementation of evidence based and effective harm reduction measures such as needle exchange services, overdose prevention centres, properly prescribed opioid substitution treatments, continuity of care for adult prisoners with a substance misuse need, and diamorphine assisted therapy; all of which have been shown to reduce the harms associated with heroin use, be cost effective, and increase contact with the medical system in marginalised populations.

**Key limitations of the current proposal:**

- Legislation allows for naloxone supply registration but doesn't mandate supply by named services, risking uneven availability.
- Prescription-only status of naloxone limits public education; exceptions for educational campaigns in high-risk areas are suggested.
- Draft amendment subject to change post public consultation ending March 6th, 2024. Consultation Link
- All previous recommendations from the ACMD should be accepted and implemented

## Naloxone Availability in Other Jurisdictions

The World Health Organization has recommended that people who may witness an overdose have access to naloxone and its associated training, also acknowledging the life-saving effect of these interventions [55].

The U.S. Food and Drug Administration licensed naloxone nasal spray for over-the-counter sales in March 2023 [56], facilitating access for family members and caregivers of people who use opioids [42]. Despite extensive education campaigns in most states, the cost of the nasal formulation is a barrier to uptake [42]. Other jurisdictions such as Australia [57], Canada [58], Italy and France [59] have made naloxone available without a prescription. Research conducted in France showed that take-home naloxone did not lead to an increase in opioid injecting frequency or risk of overdose [60].

In Scotland, naloxone availability has been greatly expanded, it was the first country globally to offer a national naloxone programme. Kits are available through the national postal service to anyone who requests them, provided they have completed the required training [61], as well as through third sector organisations such as Scottish Families Affected by Drugs and Alcohol who offer a 'click and deliver service' [62]. Naloxone is currently offered free of charge in drug treatment services in Scotland. In October 2023, Scotland announced another lifesaving overdose reversal scheme wherein all community pharmacies must have two naloxone kits in stock [63].

## Conclusion

There is an urgent and growing need to address the growing opioid crisis in the UK, particularly with the rise of potent synthetic opioids. Increasing naloxone availability is cost-effective and could play a vital role in opioid drug-related deaths, in line with the government's stated objectives in the 10-year drug strategy [64]. Several jurisdictions have greatly facilitated access to naloxone with success and the UK should rapidly follow suit. The initiation of a consultation by the Department of Health and Social Care to enhance naloxone access is a positive step, yet its scope falls short of comprehensive improvement. Historically, the pace of change in naloxone availability has been notably sluggish. It is therefore important to seize the opportunity and ensure the legislation provides equitable and consistent access to naloxone across the public.

**The call to action is clear: support legislative changes to increase the availability of naloxone and advocate for a broader approach which includes public education campaigns, guaranteed naloxone carriage in key professions such as emergency medical services and hostels.** Increased public education and access, represents a crucial step in our collective effort to reduce drug-related deaths and advance harm reduction strategies in the UK. Your support is essential in turning this proposal into a life-saving reality.

## Disclaimer

The Centre for Evidence Based Drug Policy receives funding from Ethypharm UK, a leading supplier of naloxone in the UK. An explicit stipulation of this funding is that the Centre retains complete independence in its perspectives and projects. Our recommendations and conclusions are firmly grounded on rigorously evaluated and the most reliable evidence available, ensuring unbiased and objective analysis.

## References


1. Humphreys, K. *et al.* Responding to the opioid crisis in North America and beyond: recommendations of the Stanford-Lancet Commission. *Lancet* 399, 555–604 (2022).

2. Amaducci, A. *et al.* Naloxone Use in Novel Potent Opioid and Fentanyl Overdoses in Emergency Department Patients. *JAMA Netw Open* 6, e2331264 (2023).

3. Kelly, E. *et al.* The anomalous pharmacology of fentanyl. *Br. J. Pharmacol.* 180, 797–812 (2023).

4. Hill, R., Santhakumar, R., Dewey, W., Kelly, E. & Henderson, G. Fentanyl depression of respiration: Comparison with heroin and morphine. *Br. J. Pharmacol.* 177, 254–266 (2020).

5. Zhu, D. T., Tamang, S. & Humphreys, K. Promises and perils of the FDA's over-the-counter naloxone reclassification. *Lancet Reg Health Am* 23, 100518 (2023).

6. Ujváry, I. *et al.* DARK Classics in Chemical Neuroscience: Etonitazene and Related Benzimidazoles. *ACS Chem. Neurosci.* 12, 1072–1092 (2021).

7. Lintzeris, N. Prescription of heroin for the management of heroin dependence: current status. *CNS Drugs* 23, 463–476 (2009).

8. Ferri, M., Davoli, M. & Perucci, C. A. Heroin maintenance treatment for chronic heroin-dependent individuals: a Cochrane systematic review of effectiveness. *J. Subst. Abuse Treat.* 30, 63–72 (2006).

9. *Table A6.2, Approximate potency of opioids relative to morphine; PO and immediate-release formulations unless stated otherwisea*. (World Health Organization, 2018).

10. Mather, L. E. Clinical pharmacokinetics of fentanyl and its newer derivatives. *Clin. Pharmacokinet.* 8, 422–446 (1983).

11. Tamburro, L. P., Al-Hadidi, J. H. & Dragovic, L. J. Resurgence of Fentanyl as a Drug of Abuse. *Journal of Forensic Science and Medicine* 2, 111 (2016).

12. Sutter, M. E. *et al.* Fatal Fentanyl: One Pill Can Kill. *Acad. Emerg. Med.* 24, 106–113 (2017).

13. Fentanyl drug profile. https://www.emcdda.europa.eu/publications/drug-profiles/fentanyl_en.

14. Shafer, S. L. Carfentanil: a weapon of mass destruction. *Canadian journal of anaesthesia = Journal canadien d'anesthesie* vol. 66 351–355 (2019).

15. Hikin, L., Smith, P. R., Ringland, E., Hudson, S. & Morley, S. R. Multiple fatalities in the North of England associated with synthetic fentanyl analogue exposure: Detection and quantitation a case series from early 2017. *Forensic Sci. Int.* 282, 179–183 (2018).

16. Elliott, S. P. & Hernandez Lopez, E. A Series of Deaths Involving Carfentanil in the UK and Associated Post-mortem Blood Concentrations. *J. Anal. Toxicol.* 42, e41–e45 (2018).

17. Seizures of drugs in England and Wales, financial year ending 2022. *GOV.UK* https://www.gov.uk/government/statistics/seizures-of-drugs-in-england-and-wales-financial-year-ending-2022/seizures-of-drugs-in-england-and-wales-financial-year-ending-2022.

18. Office for Health Improvement and Disparities. National Patient Safety Alert - Office for Health Improvement and Disparities. https://www.cas.mhra.gov.uk/ViewandAcknowledgment/ViewAlert.aspx?AlertID=103236 (2023).
19. ACMD advice on 2-benzyl benzimidazole and piperidine benzimidazolone opioids (accessible version). *GOV.UK* https://www.gov.uk/government/publications/acmd-advice-on-2-benzyl-benzimidazole-and-piperidine-benzimidazolone-opioids/acmd-advice-on-2-benzyl-benzimidazole-and-piperidine-benzimidazolone-opioids-accessible-version.
20. European Monitoring Centre for Drugs and Drug Addiction. European Drug Report 2023: Trends and Developments.https://www.emcdda.europa.eu/publications/european-drug-report/2023_en doi:10.2810/161905.
21. Nitazenes detected in heroin samples related to Dublin Overdose cluster. *HSE.ie* https://www.hse.ie/eng/services/news/media/pressrel/nitazenes-detected-in-heroin-samples-related-to-dublin-overdose-cluster.html.
22. McAuley, M. Nitazenes: Super strength street drugs linked to multiple NI deaths. *BBC* (2023).
23. Homer, A. & Johal, N. Street drugs stronger than heroin linked to 54 deaths in UK. *BBC* (2023).
24. Afghanistan opium cultivation in 2023 declined 95 per cent following drug ban: new UNODC survey. *United Nations : Office on Drugs and Crime* https://www.unodc.org/unodc/en/press/releases/2023/November/afghanistan-opium-cultivation-in-2023-declined-95-per-cent-following-drug-ban_-new-unodc-survey.html.
25. United Nations Office on Drugs and Crime. Afghanistan opium survey 2023 Cultivation and production after the ban: effects and implications.
26. Government response to the ACMD's advice on 2-benzyl benzimidazole and piperidine benzimidazolone opioids (accessible version). *GOV.UK* https://www.gov.uk/government/publications/acmd-advice-on-2-benzyl-benzimidazole-and-piperidine-benzimidazolone-opioids/government-response-to-the-acmds-advice-on-2-benzyl-benzimidazole-and-piperidine-benzimidazolone-opioids-accessible-version.
27. Great Britain: Parliament: House of Commons: Science and Technology Committee. *Drug Classification: Making a Hash of It?; Fifth Report of Session 2005-06; Report, Together with Formal Minutes, Oral and Written Evidence*. (The Stationery Office, 2006).
28. Viscountess Runciman DBE. Drugs and the Law: Report of the Independent Inquiry into the Misuse of Drugs Act 971. (2000).
29. UK Drug Policy Commission. The UK Drug Classification System: issues and challenges. (2008).
30. Academy of Medical Sciences. Brain science, addiction and drugs project. J. Psychopharmacol. 19, 325 (2005).
31. Kim, H. K. & Nelson, L. S. Reducing the harm of opioid overdose with the safe use of naloxone : a pharmacologic review. Expert Opin. Drug Saf. 14, 1137–1146 (2015).
32. Sgherza, A. L. et al. Effect of naloxone on perceived exertion and exercise capacity during maximal cycle ergometry. J. Appl. Physiol. 93, 2023–2028 (2002).

33. Jasinski, D. R., Martin, W. R. & Haertzen, C. A. The human pharmacology and abuse potential of N-allylnoroxymorphone (naloxone). *J. Pharmacol. Exp. Ther.* 157, 420–426 (1967).
34. Berkowitz, B. A. The relationship of pharmacokinetics to pharmacological activity: morphine,methadone and naloxone. Clin. Pharmacokinet. 1, 219–230 (1976).
35. Elzey, M. J., Fudin, J. & Edwards, E. S. Take-home naloxone treatment for opioid emergencies: a comparison of routes of administration and associated delivery systems. Expert Opin. Drug Deliv. 14, 1045–1058 (2017).
36. Peprah, K. & Frey, N. Intranasal and Intramuscular Naloxone for Opioid Overdose in the Pre-Hospital Setting: A Review of Comparative Clinical and Cost-Effectiveness, and Guidelines [Internet]. (Canadian Agency for Drugs and Technologies in Health, 2017).
37. McDonald, R. et al. Pharmacokinetics of concentrated naloxone nasal spray for opioid overdose reversal: Phase I healthy volunteer study. Addiction 113, 484–493 (2018).
38. Dietze, P. et al. Effect of Intranasal vs Intramuscular Naloxone on Opioid Overdose: A Randomized Clinical Trial. JAMA Netw Open 2, e1914977 (2019).
39. ACMD. ACMD review of the UK naloxone implementation (accessible). GOV.UK https://www.gov.uk/government/publications/acmd-naloxone-review/acmd-review-of-the-uk-naloxone-implementation-accessible (2022).
40. Yousefifard, M. et al. Intranasal versus Intramuscular/Intravenous Naloxone for Pre-hospital Opioid Overdose: A Systematic Review and Meta-analysis. Adv J Emerg Med 4, e27 (2020).
41. Skulberg, A. K. et al. Comparison of intranasal and intramuscular naloxone in opioid overdoses managed by ambulance staff: a double-dummy, randomised, controlled trial. Addiction 117, 1658–1667 (2022).
42. Jordan, M. R. & Morrisonponce, D. Naloxone. (StatPearls Publishing, 2023).
43. Advisory Council on Naloxone. Consideration of Naloxone. (2012).
44. Boyd, J. J. et al. Recurrent opioid toxicity after pre-hospital care of presumed heroin overdose patients. Acta Anaesthesiol. Scand. 50, 1266–1270 (2006).
45. Vilke, G. M., Sloane, C., Smith, A. M. & Chan, T. C. Assessment for deaths in out-of-hospital heroin overdose patients treated with naloxone who refuse transport. Acad. Emerg. Med. 10, 893–896 (2003).
46. Wampler, D. A., Molina, D. K., McManus, J., Laws, P. & Manifold, C. A. No deaths associated with patient refusal of transport after naloxone-reversed opioid overdose. Prehosp. Emerg. Care 15, 320–324 (2011).
47. Levine, M., Sanko, S. & Eckstein, M. Assessing the Risk of Prehospital Administration of Naloxone with Subsequent Refusal of Care. Prehosp. Emerg. Care 20, 566–569 (2016).
48. Langham, S., Wright, A., Kenworthy, J., Grieve, R. & Dunlop, W. C. N. Cost-Effectiveness of Take-Home Naloxone for the Prevention of Overdose Fatalities among Heroin Users in the United Kingdom. Value Health 21, 407–415 (2018).
49. Bird, S. M., McAuley, A., Perry, S. & Hunter, C. Effectiveness of Scotland's National Naloxone Programme for reducing opioid-related deaths: a before (2006-10) versus after (2011-13) comparison. Addiction 111, 883–891 (2016).

50. Townsend, T. et al. Cost-effectiveness analysis of alternative naloxone distribution strategies: First responder and lay distribution in the United States. Int. J. Drug Policy 75, 102536 (2020).
51. Coffin, P. O. & Sullivan, S. D. Cost-effectiveness of distributing naloxone to heroin users for lay overdose reversal. *Ann. Intern. Med.* 158, 1–9 (2013).
52. Cherrier, N., Kearon, J., Tetreault, R., Garasia, S. & Guindon, E. Community Distribution of Naloxone: A Systematic Review of Economic Evaluations. *Pharmacoecon Open* 6, 329–342 (2022).
53. Medicines and Healthcare products Regulatory Agency. Explanatory Memorandum to the Human Medicines (Amendment) (No. 3) Regulations 2015. (2015).
54. Proposals to expand access to take-home naloxone supplies. GOV.UK https://www.gov.uk/government/consultations/proposals-to-expand-access-to-take-home-naloxone-supplies/proposals-to-expand-access-to-take-home-naloxone-supplies.
55. World Health Organization. Opioid overdose. https://www.who.int/news-room/fact-sheets/detail/opioid-overdose.
56. Center for Drug Evaluation & Research. Information about Naloxone and Nalmefene. U.S. Food and Drug Administration https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/information-about-naloxone-and-nalmefene (2024).
57. Australian Government Department of Health & Care, A. Where to access naloxone. Australian Government Department of Health and Aged Care https://www.health.gov.au/our-work/take-home-naloxone-program/where-to-access-naloxone (2024).
58. Health Canada. Naloxone. https://www.canada.ca/en/health-canada/services/opioids/naloxone.html.
59. European Monitoring Centre for Drugs and Drug Addiction. Take-home naloxone – topic overview. https://www.emcdda.europa.eu/publications/topic-overviews/take-home-naloxone_en.
60. Colledge-Frisby, S. et al. Injection Drug Use Frequency Before and After Take-Home Naloxone Training. JAMA Netw Open 6, e2327319 (2023).
61. Naloxone Click & Deliver postal service (Free). NHS inform https://www.nhsinform.scot/scotlands-service-directory/health-and-wellbeing-services/f1289bca1f98458a84c97fae962f364d%201.
62. Scottish Families Affected by Drugs and Alcohol. Our 'click & deliver' take-home naloxone service is now live. https://www.sfad.org.uk/our-click-deliver-take-home-naloxone-service-is-now-live.
63. Scottish Government. Lifesaving overdose-reversal scheme.
64. Government, H. M. From harm to hope: a 10-year drugs plan to cut crime and save lives. Preprint at (2021).

FEBRUARY 2024


ALEX.PIOT@DRUGPOLICYCENTRE.ORG

WWW.DRUGPOLICYCENTRE.ORG

@DRUGPOLICYUK



ALEXANDRE PIOT

Centre for Evidence Based Drug Policy