# Synthetic Opioid Preparedness

## Fact sheet for medical care providers

February 2024

**This update has been developed by the HSE National Clinical Lead for Addiction Services and the National Red Alert Group (NRAG) in response to the emergence of N-pyrrolidino protonitazene on the Irish drug market. This fact sheet is dated February 2024 with the content and guidance subject to change based on possible future developments in this area.**

**The NRAG is coordinated by the HSE National Clinical Lead for Addiction Services and includes representatives from the National Social Inclusion Office, the National Ambulance Service Director, Dublin Fire Brigade, the HSE National Drug Treatment Centre Laboratory, the Garda National Drugs and Organised Crime Bureau, Forensic Science Ireland, the State Laboratory, hospital network ED representative and Pharmacology and Therapeutics, School of Medicine, Trinity College Dublin. The aim of the NRAG is to monitor signals of change such as increases in overdoses or drug market shifts and to rapidly respond to future outbreaks, should they occur.**

## The emergence of N-pyrrolidino protonitazene on the Irish drug market

Two outbreaks of overdose clusters have occurred since the 9th of November 2023 as a result of the emergence of the substance N-pyrrolidino protonitazene on both the Dublin and Cork heroin markets. As of the date of publication, a total of 57 non-fatal overdoses were reported to the HSE during the period of the 9th – 14th of November and a further 17 were reported over a 6 day period in the Cork Region at the start of December.

At this moment in time, it is too early to speculate as to what extent nitazenes will become established on the Irish drugs market, but this is an area that now requires intensive monitoring by health care providers and law enforcement given the serious public health threat posed by these compounds. Of particular concern is the emergence of nitazenes sold as falsified medicines (mainly oxycodone as blue or yellow tablets and as benzodiazepines) in the UK. While less common, they have been sold as cocaine and cannabinoids, as well as in liquid form [1].

Since the outbreak periods, a second alert was issued by the HSE (dated 2nd February 2024) following the identification of a second and new batch of nitazenes (Protonitazene). The HSE advised that there is now a risk of nitazenes presenting in a variety of different coloured powders.



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## Nitazene type drugs (benzimidazoles)

Nitazenes are potent synthetic opioids (derived from 2-benzylbenzimidazole) which are newly emerging on the American and European drugs market but were first developed during the mid-1950s through attempts to produce better and safer opioid analgesics [2]. Nitazenes are μ-opioid receptor agonists with effects comparable to those of other μ-opioid receptor agonists, such as morphine, oxycodone, heroin etc. [3]. The nitazene family consists of numerous analogs with the potential for more analogs to be added. To contextualise the risks posed, these compounds have the levels of analgesic potency several orders of magnitude higher than that of morphine [2]. Many are at least as potent as fentanyl, some are more potent. The first nitazene opioid identified on the European drug market was isotonitazene in 2019. It was risk assessed by the EU Drugs Agency (The EMCDDA) in 2020 based on concerns over its potential to spread and cause life-threatening poisoning. As of 22 December 2023, the EMCDDA has formally notified 16 nitazenes that have been identified on the European drug market since 2019 [4].

### Common nitazenes recently identified in Europe include:

- **Isotonitazene**
- **Metonitazene**
- **Etonitazene**
- **Protonitazene**
- **N-pyrrollidino protonitazene**
- **N-desethyl isotonitazene**
- **N-pyrrolidino protonitazene**

N-Pyrrolidino protonitazene is a new synthetic opioid and one of the latest to emerge among the nitazene analogue (2-benzylbenzimidazole) subclass. Recently acquired in vitro pharmacological data show that N-pyrrolidino protonitazene is an active opioid with potency approximately 25 times greater than that of fentanyl [4].

## Planning for future outbreaks

The emergence of any new drug to the local market creates burdens for first responders and emergency healthcare providers as they encounter the first overdose cases without the benefit of knowing much about the pharmacology, toxicology, potential use or interactions of these novel agents. The lethal doses for nitazenes in humans, particularly in combination with other drugs or medical conditions, are not yet fully known. Many factors influence overdose-related morbidity and mortality, including not only the drug, but also the amount taken, polysubstance use, possible drug-drug interactions or drug-alcohol interactions, body weight, opioid tolerance, and underlying health status [3].

Nitazenes can lead to unexpected and sudden overdose outbreaks. To help reduce harm and protect life, emergency service providers and hospitals are advised on the requirement for additional doses of naloxone to treat nitazene and other synthetic opioid overdose presentations, with preparations now required to ensure medical service providers have adequate supplies of naloxone should outbreaks begin to occur nationally.

## Monitoring and reporting the emergence of nitazenes in medical settings

Given the limited information available on nitazenes and N-pyrrolidino protonitazene on the EU drug market, it is important to document possible cases among your patients as well as sudden increases in opioid overdoses among your patient group.

Below areas are of significance for monitoring and review of outbreaks at this time:

- The number of suspected presentations (if clusters begin to present)
- The patient's symptoms
- Naloxone dosing and titration
- Additional treatment provided and patient recovery (if felt necessary)
- If the person is suspected to not be an opioid user but displays the symptoms of an opioid overdose (for example, if the use of other drugs are reported such as tablets, stimulants, dissociatives, psychedelics or cannabinoids)
- Fatalities possibly linked with nitazene exposure that require further review
- Sample access (if paraphernalia, the substance itself and biological samples are available related to the possible case(s))

As N-pyrrolidino protonitazene is currently under intensive monitoring by the Europe Monitoring Centre for Drugs and Drug Addiction (EMCDDA) the primary nitazene detected on the Irish drug market, it is important to document and report on cases of concern or sudden overdose clusters in your area.

Hospitals nationally will be advised to report through local HSE CHO managers and local monitoring groups or alternatively directly to NRAG should that monitoring structure not be in place with your organisation. Please contact nicki.killeen@hse.ie, alternatively, please contact the National Poisons Information on 01 8379964/6. This phone line will be in operation 8am to 10pm 7 days a week.

Data from emergency service providers will be collated internally and shared with the NRAG.

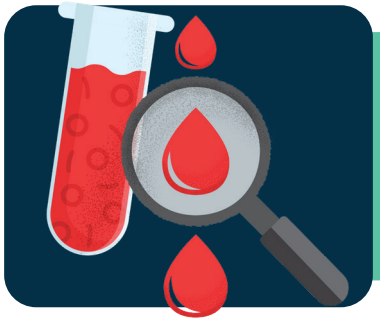
## Sample collection and laboratory analysis

Sample collection and analysis are essential in cases of overdose clusters. The drug itself, paraphernalia (used syringes, spoons and bags) and biological samples can provide essential insight on the situation emerging.

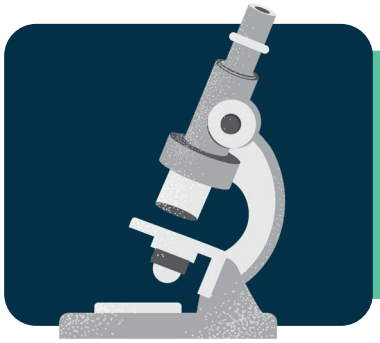
**Appropriate PPE should be used when handling suspected synthetic opioids. They should be stored in an appropriate unused, clean container and securely stored away from staff and patients.**

Used syringes should be safely collected in line with internal sharps policies and stored in an individual and secure container that can be re-opened.

Supply bags, cookers/spoons can also be considered for analysis once safely stored. Store any paraphernalia used by the patient safely using PPE as the remainder of the drug may be present.



Biological samples (Urine and blood) should be taken as soon as possible and stored safely in a fridge/freezer if possible should review be required.



Through the NRAG, the HSE National Drug Treatment Centre Laboratory can be contacted should the hospital lab want to further discuss sample storage and the movement of samples.

The review and transportation of samples should be discussed with local HSE CHO Managers and local monitoring groups or alternatively directly with NRAG if local structures are not place. Please contact nicki.killeen@hse.ie directly or the National Poisons Information Centre on 01 8379964/6. This phone line will be in operation 8am to 10pm 7 days a week.

## Management differences between heroin and synthetic opioid overdoses

### Symptoms

The below details possible signs and symptoms of synthetic opioid toxicity.

| Synthetic opioid toxicity | Severe opioid toxicity | Sudden-onset chest wall rigidity may be associated with increased risk of mortality |
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| Miosis (pinpoint pupils) | Respiratory and central nervous system depression | In comparison with heroin, intoxication with synthetic opioids and analogues presents with:<br>• increased risk of overdose<br>• more rapid onset of overdose<br>• more rapid progression of signs and symptoms |
| Nausea, vomiting | Decreased consciousness | |
| Anxiety, agitation | Apnoea | |
| Euphoria, dysphoria | Can lead to deep coma, convulsions and respiratory arrest | |
| Hallucinations, paranoia | Sudden-onset chest wall rigidity may be associated with increased risk of mortality | |

[5]

The pathophysiology of polysubstance toxidromes involving opioids, asphyxial death, and prolonged hypoxemia leading to global ischemia (cardiac arrest) differs from that of sudden cardiac arrest. People who use opioids may also develop bacteremia, central nervous system vasculitis and leukoencephalopathy, torsades de pointes, pulmonary vasculopathy, and pulmonary edema [6].

In a review of 'Naloxone Use in Novel Potent Opioid and Fentanyl Overdoses in Emergency Department Patients' patients experiencing an overdose following the consumption of the nitazene metonitazene experienced cardiac arrest and death at a higher rate than those involving other substances [7].

## Management

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

- There is a need to call emergency services and transfer to hospital, especially in cases where naloxone is not available in the community, or if there is need for additional naloxone administration.
- Treat suspected cases as for any opioid overdose, using naloxone and appropriate supportive care.
- Recognise the duration of action of naloxone is shorter than that of many opioids and appropriate monitoring and further doses of naloxone may be required.

- A more rapid escalation of additional doses of naloxone may be needed in comparison with heroin or other opioids. Overall, higher doses of naloxone may be needed which could deplete supplies if an outbreak presents.
- A longer period of observation is advised for patients.

[5]

Clinical outcomes from overdose of novel potent opioids, specifically nitazenes are unknown aside from small case series. In a recent review of 'Naloxone Use in Novel Potent Opioid and Fentanyl Overdoses in Emergency Department Patients', the novel potent opioid group received a statically higher mean of naloxone boluses in hospital compared to the fentanyl cases included in the study [8]. Metonitazene overdose was associated with cardiac arrest and more naloxone doses overall.

Medical providers are advised that responses to nitazenes may be more complex and require continued dosing of naloxone. At the time of publication, there is no guidance on how much naloxone is required and this should be treated on a case by case basis.

Any cases of concern among medical care providers should be documented and reported to help NRAG develop future guidance on this emerging area.

Given the urgent and evolving nature of this situation, further and specialist updates will be published by the National Red Alert Group to help inform and improve local and European responses.


Heroin compared to nitazene powder

## Resources for medical care providers

- The Centre for Forensic Science Research & Education. [CSFRE] US public alerts: https://www.cfsre.org/nps-discovery/public-alerts/new-nitazene-analogue-n-pyrrolidino-protonitazene-impacting-drug-markets-in-north-america-and-europe
- UK and Scottish advisory https://www.sehd.scot.nhs.uk/publications/DC20230727Opioids.pdf
- Naloxone use in novel potent opioid and fentanyl overdoses in emergency department patients. https://www.drugsandalcohol.ie/39469/
- Toxbase (2023). Naloxone – severe opiate induced respiratory depression. www.toxbase.org, accessed on 14th December 2023.
- HSE Drugs.ie 'Synthetic opioid preparation' https://www.drugs.ie/synthetic_opioid_preparation/
- The National Poisons Information Centre provides information to doctors and healthcare professionals, to assist them in the management of acute poisoning. Please contact the National Poisons Information Centre on 01 8379964/6 in cases of patients with severe/ unusual features or if multiple patients present together. This phone line will be in operation 24 hours and 7 days a week. See also poisons.ie/professionals/

## References


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# Additional supporting information

Where concerning or dependent use has been identified, signpost or refer to specialist drug treatment and recovery services, a list of national services can be found on online at **www.drugs.ie/services**

Information about different types of drugs and how to minimise harm can be found on the **Drugs.ie** website.

The **HSE Drug and Alcohol Helpline** is available to offer information and support to people who use and their loves ones on Freephone **1800 459 459** or through email at **helpline@hse.ie** Monday – Friday 9:30am – 5:30pm.

Official HSE updates on the emergence of synthetic opioids in Ireland can be found on **Drugs.ie** or through **@drugs.ie** social media channels.