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Clinical Toxicology of Novel Synthetic Opioids (Nitazenes and Emerging Fentanyl Analogues): Toxicokinetics, Toxicodynamics, Diagnosis, Management, and Public Health Challenges

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Abstract:

One of the most deadly and quickly developing risks in the current opioid crisis are novel synthetic opioids (NSOs), such as nitazenes and newly developed fentanyl analogues. Nitazenes were first synthesised in the 1950s but were never approved for clinical use. Since 2019, they have alarmingly reappeared in the illicit drug supply, showing pharmacological characteristics that defy traditional toxicological management paradigms and potencies that may surpass carfentanil in some analogues. Using the PubMed/MEDLINE, EMBASE, Scopus, and Web of Science databases, a thorough narrative review of peer-reviewed literature covering publications from 2015 through May 2026 was carried out. Reports from the United Nations Office on Drugs and Crime (UNODC), the Drug Enforcement Administration (DEA), the European Monitoring Center for Drugs and Drug Addiction (EMCDDA), and national public health agencies were also included. At the mu-opioid receptor (MOR), NSOs function as complete, very effective agonists. Nitazenes also show distinctively delayed receptor dissociation kinetics, which cause severe and protracted respiratory depression. Rapid hepatic metabolism by polymorphic CYP2D6 and CYP2B6 enzymes is revealed by toxicokinetic tests, with intrinsic clearance values that are on par with or higher than those of testosterone. Liquid chromatography-tandem mass spectrometry (LC-MS/MS) and high-resolution mass spectrometry (HRMS) continue to be the gold standards for diagnosis; traditional immunoassay-based urine drug screenings consistently fail to identify NSOs. Partial or total naloxone resistance complicates clinical therapy, requiring high cumulative doses (up to 10–20 mg) and extended observation times. NSOs provide a paradigm-shifting risk to public health infrastructure and toxicological practice. Expanding toxicological screening capabilities, modifying naloxone delivery methods, integrating harm reduction programs, and coordinating worldwide regulatory response to the constantly changing environment of new opioid analogues are all urgent issues.

Keywords: Novel Synthetic Opioids (NSOs), Nitazenes, Fentanyl Analogues, μ-Opioid Receptor, Respiratory Depression, Naloxone Resistance, Toxicokinetics, LC-MS/MS, High-Resolution Mass Spectrometry (HRMS), Harm Reduction; Drug Surveillance, Opioid Crisis

1. INTRODUCTION

The rapid rise of novel synthetic opioids (NSOs), which have significant opioid receptor activation but minimal structural resemblance to conventional opioids, is indicative of the fourth wave of the global opioid pandemic. The toxidromic effects of these NSOs are disastrous. While illicitly manufactured fentanyl (IMF) and its structural

analogues dominated the crisis through the 2010s and early 2020s, causing unprecedented overdose mortality throughout North America and Europe, nitazenes, a structurally distinct class of 2-benzylbenzimidazole opioids, have emerged as a parallel and increasingly dominant threat. [1, 9, 39]

The United Nations Office on Drugs and Crime (UNODC) Early Warning Advisory states that isotonitazene became the first unscheduled nitazene in 2019. Since then, the number of different nitazene analogues reported to international monitoring systems has grown from one molecule in 2019 to more than 13 distinct chemical entities by 2023. Six novel nitazenes were found in 2024 alone.[8] By early 2025, nitazenes were discovered in toxicological specimens in 19 countries throughout Asia, Europe, North America, Oceania, and South America, suggesting a truly global public health emergency.[9]

NSOs provide a range of toxicological challenges. Because of their extreme potency, nanogram doses can be lethal; certain nitazene analogues are thought to be 500–1,500 times more potent than morphine, while carfentanil has a potency that is 10,000 times more than that of morphine [4,17]. Unlike heroin or prescription opioids, NSOs are not detected by conventional immunoassay-based urine drug testing. This results in a diagnostic blind spot that impacts emergency response, toxicological evaluation, and epidemiological surveillance.Furthermore, compared to heroin or conventional fentanyl overdoses, nitazenes' slow receptor dissociation kinetics have been associated with clinically significant naloxone resistance, requiring longer observation periods and higher cumulative antagonist dosages [5,6,14].

This study examines the clinical toxicity of nitazenes and developing fentanyl analogues, the two most clinically and epidemiologically significant NSO classes, as well as brorphine-related compounds (orphines), an emerging third class. Methodically discussed are the historical context, structural pharmacology, toxicokinetics, toxicodynamics, clinical presentation, diagnostic methods, acute and subacute management choices, and the broader public health and regulatory challenges they bring.

2. HISTORICAL CONTEXT AND CLASSIFICATION

2.1 Historical Development of Synthetic Opioids

Synthetic opioids' history is intertwined with both illicit use and medical advancement. Fentanyl was first developed by Paul Janssen in 1960 as a phenylpiperidine derivative of meperidine, which has a strong anaesthetic effect and a rapid onset.[17] Later decades saw the development of other pharmacological fentanyl alternatives, including remifentanil, sufentanil, and alfentanil, each of which was designed for specific therapeutic contexts. The illegal appropriation of fentanyl chemistry began with the covert synthesis of alpha-methylfentanyl in the 1980s, and it accelerated in the 2010s with the rise of large-scale illicit manufacture in China.[12, 26]

Nitazenes have a similar but lesser-known history. Etonitazene was first synthesised in the late 1950s by researchers at CIBA Aktiengesellschaft (Switzerland) as part of a hunt for novel analgesics.[5, 7] Pharmacological studies soon revealed a restricted therapeutic index, a considerable tendency toward addiction, and potency that was significantly greater than that of morphine. Consequently, before any of the substances were used in clinical settings, the class was

totally discontinued.[18] Although clonitazene and etonitazene were classified in the United Nations Single Convention on Narcotic Drugs in 1961, the class was mostly uncontrolled worldwide until 2019, creating a regulatory gap that clandestine chemists exploited. [5,21]

China increased restrictions on the manufacture of fentanyl analogues in 2019, which reduced the availability of the most common illicit synthetic opioids and promoted the chemical adaptability demonstrated by nitazene synthesis. The resurgence of nitazenes coincided with this.[1, 19] Therefore, the fourth wave of the opioid pandemic shows the continued demand for potent illicit opioids as well as the capacity of illicit markets to swiftly innovate past legislative restrictions.[39]

2.2 Structural Classification of NSOs

Novel synthetic opioids may be roughly categorised using two fundamental structural classes and many emerging groups. Fentanyl analogues, such as acetylfentanyl, carfentanil, furanylfentanyl, ocfentanil, butyrylfentanyl, 3-methylfentanyl, and other fluorinated derivatives, are defined by the phenethyl-4-piperidyl benzamide (phenylpiperidine) scaffold.[13,17] Nitazenes (benzimidazole opioids), which include isotonitazene, protonitazene, metonitazene, etonitazene, butonitazene, flunitazene, and metodesnitazene, are defined by the 2-benzylbenzimidazole core.[5,10] Emerging orphine analogues (cychlorphine, spirochlorphine), which were first identified in 2024–2025, offer a third class and appear to address market gaps created by nitazene regulatory restrictions.[31, 33]

Table 1 summarises the classification, representative compounds, relative potencies, and scheduling status of the major NSO classes.

Table 1. Classification of Major Novel Synthetic Opioid Classes

Class	Representative Compounds	Potency vs. Morphine	Legal Status	First Reported
Fentanyl Analogues	Acetylfentanyl, Carfentanil, Furanylfentanyl, Ocfentanil, Butyrylfentanyl, 3-Methylfentanyl	50–10,000× morphine	Mostly Schedule I (US); varies internationally	1980s–2010s
Nitazenes (Benzimidazoles)	Isotonitazene, Protonitazene, Metonitazene, Etonitazene, Butonitazene, Flunitazene, Metodesnitazene	10–1,500× morphine; some exceed carfentanil	10 analogues internationally scheduled as of 2025; others emerging	2019 (isotonitazene)

Brorphine Analogues (Orphines)	Cychlorphine, Desmethylchlorphine, Spirochlorphine	Estimated very high; data limited	Emerging; largely unscheduled	2024–2025
Benzamide NSOs	U-47700, AH-7921	~7.5× morphine (U-47700)	Schedule I (US)	2015–2016

3. TOXICOKINETICS

3.1 Absorption

The many routes of unlawful NSO exposure have a considerable impact on the rate and intensity of toxicological consequences. By getting the whole dose into systemic circulation in a couple of seconds, intravenous injection results in almost instantaneous receptor occupancy in the central nervous system (CNS). Nasal insufflation and vaping/inhalation offer rapid absorption through mucosal membranes and pulmonary vasculature, with an average onset time of one to five minutes.[2,26] Clinical case studies from Australia have demonstrated that vaping is a prevalent method of nitazene exposure in addition to injection and oral ingestion.[2]

The high lipophilicity of both fentanyl analogues and nitazenes, which is represented in estimated LogP values of 3.8–5.0 for most compounds, enables rapid penetration of biological membranes, including the blood-brain barrier.[23, 26] After any systemic exposure pathway, this physicochemical property and low molecular weights (often between 300 and 500 Da) enable extraordinarily rapid CNS penetration. This pharmacokinetic profile is in line with the potent, nearly instantaneous effects that users of nitazenes or fentanyl generated illegally have described.[23]

3.2 Distribution

About 80–85% of fentanyl is attached to plasma proteins, mainly alpha-1-acid glycoprotein and albumin. Its large distribution volume (4-6 L/kg) suggests significant tissue sequestration in adipose and skeletal muscle. [23, 26] Peripheral compartment sequestration is crucial from a clinical standpoint because, when plasma concentrations rapidly decline after absorption, peripheral stores may redistribute back into circulation, producing secondary peaks (the "fentanyl rebound" phenomenon) that account for recurrent respiratory depression after initial naloxone reversal.[23]

Toxicokinetic data for nitazenes in humans are mostly derived from in vitro studies and extrapolations due to ethical and legal limitations on interventional human pharmacokinetic research with Schedule I medications.[7, 13] The clinical observation that nitazene overdoses result in prolonged and recurrent respiratory depression that lasts much beyond the length of the naloxone effect is consistent with a distribution kinetic profile that sustains CNS drug concentrations long after systemic plasma levels decline.[2, 6, 36]

3.3 Metabolism

Hepatic biotransformation, the primary route for NSO metabolism, is principally mediated by the cytochrome P450 (CYP) enzyme system. The N-dealkylation of fentanyl, which produces the pharmacologically inactive molecule

norfentanyl, is mostly carried out by CYP3A4.[23,26] Carfentanil is hydrolysed by esterases and CYP enzymes to yield norcarfentanil and other metabolites.[4]

Nitazene metabolism has been studied using primary human hepatocytes and recombinant CYP isoforms. The primary enzymes identified are CYP2D6, CYP2B6, and CYP2C8 [7,34]. CYP2D6 alone depleted butonitazene by 99% and isotonitazene by 72% after 30 minutes, according to in vitro incubations.[7] Among the metabolic pathways are phase II conjugation reactions such hydroxylation of aromatic and aliphatic rings, N-dealkylation of the aminoalkyl side chain, and glucuronidation and acetylation.[13] The intrinsic clearance values of butonitazene, isotonitazene, and protonitazene (14.4, 15.2, and 16.0 mL/min/g liver, respectively) demonstrate moderate-to-high hepatic extraction when compared to reference medications such as testosterone.[13]

Polymorphic CYP enzymes, particularly CYP2D6, which has well-known broad, intermediate, and poor metaboliser profiles, contribute to inter-individual variation in susceptibility to nitazene toxicity.[7,34] Individuals with impaired metabolism may have much higher and more persistent plasma drug concentrations, increasing the risk of overdose.[7]

Table 2 summarises available toxicokinetic parameters for the major NSO compounds.

Table 2. Comparative Toxicokinetic Parameters of Major Novel Synthetic Opioids

Compound	Primary CYP	Intrinsic Clearance (mL/min/g liver)	Key Metabolites	LogP (est.)	Half-life (est.)
Fentanyl	CYP3A4	~11–16	Norfentanyl	4.05	219 min (IV)
Carfentanil	CYP3A4	High (est.)	Norcarfentanil	3.80	~7 h (est.)
Isotonitazene	CYP2D6, CYP2B6	15.2	Monohydroxy, N-desethyl metabolites	~4.8 (est.)	Not established
Protonitazene	CYP2D6, CYP2C8	16.0	Hydroxylated, glucuronidated metabolites	~4.6 (est.)	Not established
Butonitazene	CYP2D6, CYP2B6	14.4	Hydroxylation, N-dealkylation products	~4.5 (est.)	Not established
Metonitazene	CYP2D6 (likely)	High (est.)	Demethylated, hydroxylated metabolites	~4.3 (est.)	Not established

3.4 Elimination

A little quantity of fentanyl is excreted unchanged in the urine, with the remaining 75% being eliminated as norfentanyl and other hydroxylated metabolites.[23, 26] The elimination half-life is route-dependent and is about 219 minutes after intravenous administration but 7 hours following buccal or transmucosal dosing due to slow mucosal release. The elimination half-lives of carfentanil and other analogues with greater lipophilicity may be significantly longer.[4, 25]

Although there is currently a lack of quantitative elimination data in humans, the primary excretory mechanism for nitazenes is believed to be urinary elimination of both the parent chemical and its metabolites.[7,13] The extended duration of clinical toxicity in cases of nitazene overdose, which often lasts 12 to 24 hours or more, indicates that receptor binding kinetics have a significant role in the duration of effect beyond hepatic clearance alone.[2, 6, 36]

4. TOXICODYNAMICS

4.1 Molecular Mechanisms: Opioid Receptor Pharmacology

The primary molecular target of all clinically significant NSOs, which operate via agonism at opioid receptors, is the mu-opioid receptor (MOR, encoded by the OPRM1 gene).[15,16] MOR is a class A G protein-coupled receptor (GPCR) that mainly communicates by activating Gi/Go proteins, which leads to: activation of G protein-coupled inwardly rectifying potassium (GIRK) channels, which results in the hyperpolarisation of neurones; inhibition of voltage-gated calcium channels, which suppresses the release of neurotransmitters; and inhibition of adenylyl cyclase and reduction of cAMP.[15, 27]

When compared to conventional opioids, NSOs show unusually high intrinsic efficacy at MOR and act as full superagonists in G protein signalling tests.[15,27] In vitro functional profiling studies employing BRET-based assays show that fentanyl and nitazene analogues have maximal G protein activation that significantly outperforms the intrinsic efficacy of morphine or buprenorphine.[15] This high efficacy has direct therapeutic significance because of the steep and narrow dose-response curves that allow little room between an inebriated and lethal dosage.[16]

4.2 Nitazene-Specific Receptor Kinetics: The Slow Dissociation Phenomenon

One characteristic of nitazene pharmacodynamics that is both mechanistically distinct and clinically relevant is the delayed dissociation kinetics of nitazene from the MOR. Nitazenes have substantially longer receptor-bound states than fentanyl and morphine, which swiftly dissociate from receptor binding sites, according to pharmacological study.[6] Because of its slow off-rate (koff), the competitive antagonist naloxone finds it significantly more difficult to displace the agonist and restore receptor activity when nitazenes occupy MOR.[6, 33]

This kinetic resistance to naloxone reversal, which is fundamentally different from competitive resistance based just on relative potency, explains an important clinical observation. Nitazene-induced respiratory depression may only be temporarily or insufficiently reversed by standard or even somewhat high naloxone dosages.[3, 6] This has been independently confirmed by several in vitro pharmacology studies, and it is consistent with clinical case series that

demonstrate patients who overdose on nitazenes require longer hospital stays and higher cumulative naloxone doses (10–20 mg), often requiring mechanical respiration.[2, 3, 24]

4.3 Organ System Effects

4.3.1 Respiratory System

Respiratory depression, which is brought on by MOR-mediated control of neurones in the brainstem's pre-Botzinger complex (preBotC), is the main lethal mechanism of NSO poisoning.[16, 32] After a high-potency NSO overdose, respiratory arrest may happen extremely quickly, before any opportunity for assistance. The wooden chest syndrome, a form of severe muscular rigidity that affects the thorax and abdomen and literally prevents breathing, is a documented adverse effect of high-dose fentanyl. This state can also be brought on by nitazenes, which makes neuromuscular blocking necessary for successful intubation.[4, 28]

4.3.2 Cardiovascular System

The cardiovascular effects of opioids include bradycardia (induced by vagal stimulation and direct effects on sinoatrial node conduction), hypotension (produced by peripheral vasodilatation and reduced cardiac output owing to hypoxia), and, in situations of severe overdose, cardiac arrest. Carfentanil and other nitazene analogues have been associated with refractory cardiac arrest, which is often preceded by severe hypoxia. ECG abnormalities, including as QT prolongation, have been seen with a number of NSO analogues. These abnormalities may suggest additional ion channel interactions beyond basic MOR agonism.[4, 18]

4.3.3 Central Nervous System

Progressive central nervous system depression manifests as sedation, slurred speech, ataxia, stupor, and coma. Pupillary miosis, or bilateral pinpoint pupils, is a common characteristic that is mediated by MOR agonism in the Edinger-Westphal nucleus and is a reliable clinical sign when it occurs.[32,29] Non-cardiogenic pulmonary oedema is another dangerous effect that is thought to be brought on by a combination of opioid-mediated changes in pulmonary capillary permeability and hypoxia-driven catecholamine surges.[4,16]

4.3.4 Gastrointestinal and Other Systems

Constipation, nausea, and vomiting are brought on by MOR activation in the gastrointestinal tract, which increases sphincter tone and decreases peristalsis. When an obtunded patient with an acute overdose vomits, there is a significant risk of aspiration. Urinary retention is caused by inhibition of the voiding reflex. Hypothermia may result from hypothalamic dysfunction and peripheral vasodilatation. Overdoses that go unnoticed often cause prolonged immobility, which might end in rhabdomyolysis. [29, 32]

5. CLINICAL PRESENTATION AND TOXIDROME RECOGNITION

5.1 The Classic Opioid Toxidrome and NSO Variations

The classic opioid toxidrome consists of three elements: miosis, respiratory depression, and CNS depression (from drowsiness to coma). This presentation is usually relevant to NSO intoxications, despite some notable quantitative and qualitative variances. Respiratory depression usually occurs faster and is more severe than heroin or oral opiates. Particularly when nitazenes are taken, CNS and respiratory depression lasts significantly longer.[2, 18]

An Australian clinical case study revealed 27 nitazene exposures with laboratory confirmation between June 2018 and March 2025 (Roberts et al., 2025).[2] Of the 20 cases of acute poisoning, vaping was the most common form of exposure, followed by ingestion, injection, and nasal insufflation. Acute poisoning frequently resulted in sedation and hypoventilation; in severe cases, endotracheal intubation was required due to hypoxia or cardiac arrest.[2] In seven cases where nitazene was the primary medication used, physical reliance was indicated by indicators of opioid withdrawal rather than acute intoxication.[2]

5.2 Polysubstance Toxicity

The prevalence of NSOs in the context of polysubstance use greatly complicates clinical management.[29,32] Co-ingestants in NSO overdose instances often include alcohol, cocaine, xylazine, benzodiazepines, and other stimulants.[37] Because benzodiazepines and xylazine (an alpha-2 adrenergic agonist veterinary drug frequently used as an adulterant in the US illicit drug supply) potentiate CNS and respiratory depression through non-opioid mechanisms, they are not reversible by naloxone, increasing the minimum effective naloxone dose required while also making full reversal impossible.[37, 39]

5.3 Differentiation from Other Toxidromes

Important differentials for NSO overdose include organophosphate poisoning, hypertensive encephalopathy, sedative-hypnotic intoxication, and GHB intoxication. The most accurate method of confirming opioid toxidosis is a positive clinical response to naloxone. However, as certain NSOs exhibit a partial or absent naloxone response, as was previously indicated, naloxone responsiveness alone cannot be utilised to detect toxidrome.[3, 6, 24]

Table 3 presents a comparative clinical overview of NSOs versus classical opioids.

Table 3. Comparative Clinical Features of NSOs versus Classical Opioids

Clinical Parameter	Fentanyl / Analogues	Nitazenes	Classic Opioids (Heroin/Morphine)
Onset of Action	Seconds–minutes (IV); 1–5 min (insufflation)	Rapid; route-dependent (minutes)	2–5 min (IV); 10–30 min (oral)
Duration of Effect	30–90 min (varies by analogue)	Prolonged; often >6–12 h	3–5 h (heroin/morphine)

Respiratory Depression	Severe; rapid onset	Severe; prolonged; may be refractory	Moderate–severe
Naloxone Responsiveness	Usually responsive; repeated doses needed for potent analogues	Partial to resistant; multiple high doses required	Typically responsive to standard doses
CNS Effects	Sedation, coma, miosis	Deep sedation, coma, miosis; prolonged	Euphoria, sedation, miosis
Muscle Rigidity	Wooden chest syndrome (high dose)	Reported; frequency unclear	Uncommon
Standard Immunoassay Detection	Fentanyl: partial; analogues: usually NOT detected	NOT detected by standard opioid screens	Yes (morphine/heroin)
Withdrawal Syndrome	Rapid onset (4–8 h), short duration	Similar to opioid withdrawal; prolonged in some cases	Onset 8–24 h; duration 5–7 days

6. DIAGNOSIS AND ANALYTICAL TOXICOLOGY

6.1 Limitations of Standard Urine Drug Screens

Conventional immunoassay-based urine drug screens (UDS) are designed to detect opioid drugs by cross-reactivity using antibody panels calibrated against morphine, codeine, and semisynthetic opioids. The chemically distinct 2-benzylbenzimidazole core of nitazenes exhibits no discernible cross-reactivity with these panels. Numerous independent studies have shown that nitazenes routinely provide negative results on standard opioid immunoassays, even at amounts well beyond the lethal dosage.[5, 14] The same limitation applies to most fentanyl analogues: structural alterations in compounds such as carfentanil, furanylfentanyl, and acetylfentanyl frequently result in false-negative or unclear results.[4, 10]

There are important clinical implications for this diagnostic blind spot. When a patient appears in an emergency room with opioid toxidrome and a negative UDS, the doctor may mistakenly assume that opioids are not the cause, withhold or postpone naloxone, and neglect to look into NSO exposure.[14, 24] The fact that NSO contributions to mortality are substantially underestimated in nations that rely on immunoassay screening for overdose deaths linked to "unknown substances" is another monitoring consequence.[8,9]

6.2 Confirmatory Analytical Methods

6.2.1 Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS)

Targeted LC-MS/MS, which offers sub-nanogram per millilitre sensitivity, is now the clinical and forensic gold standard for NSO identification and quantification since blood concentrations in fatal overdose cases are frequently documented in the low ng/mL range or below.[1,14] Targeted assays must contain specific multiple reaction monitoring (MRM) transitions for each analyte; the ever-evolving NSO landscape requires regular assay panel changes to accommodate newly identified compounds.[10, 11]

6.2.2 High-Resolution Mass Spectrometry (HRMS)

Liquid chromatography–high-resolution mass spectrometry (LC-HRMS), which employs Orbitrap or quadrupole time-of-flight (QTOF) equipment, is the most efficient technique for comprehensive NSO detection, including the identification of previously unknown analogues.[1, 12] When novel compounds are found, spectral libraries may be retroactively analysed, and HRMS provides accurate mass measurements that allow molecular formula determination. Because it enables the retroactive confirmation of previously unidentified NSO exposures, this technique is highly helpful in forensic post-mortem toxicology.[12, 14]

6.2.3 Sample Selection in Clinical Practice

Urine is the most often collected matrix with a wide detection window. Whole blood collected at the time of presentation is appropriate for quantitative forensic investigation.[11,14] When NSO exposure is clinically suspected in an emergency, doctors should keep entire blood (10 mL EDTA and serum separator tubes), urine (20 mL), and, if possible, stomach aspirate for additional confirmatory study, even if routine UDS is required concurrently.[10, 11]

6.3 Point-of-Care and Drug Checking Services

Fentanyl test strips (FTS) can detect fentanyl in residual drug samples and provide harm reduction advantages in community settings, however they do not reliably detect nitazenes.[40] The susceptibility of each molecule to certain fentanyl mimics varies. Drug testing services that employ portable mass spectrometry (including ion trap and DART-QTOF instruments) provide a more analytically thorough method. Numerous European countries are using these services in harm reduction contexts, and North American pilot programs are progressively using them.[30, 33]

Table 5 summarises available analytical methods and their respective applications, sensitivity, and appropriate settings.

Table 5. Summary of Analytical Methods for NSO Detection

Method	Application	Sensitivity	Specificity for NSOs	Setting
Immunoassay (IA)	Urine drug screening	High (for target)	Very low – FAILS for NSOs	Clinical/ED

GC-MS	Forensic confirmation	Moderate–High	Moderate	Forensic
LC-MS/MS (Targeted)	Quantitative confirmation of known NSOs	Very High (sub-ng/mL)	High for included analytes	Reference Lab
LC-HRMS (QTOF/Orbitrap)	Retrospective screening; unknown compound identification	Extremely High	Very High – preferred	Reference Lab
NSO-specific Lateral Flow Strips	Point-of-care drug checking	Moderate	Limited current analyte range	Harm Reduction
Wastewater Epidemiology	Population-level surveillance	High (population)	Depends on method	Public Health

7. CLINICAL MANAGEMENT

7.1 Pre-hospital and Emergency Response

The fundamentals of pre-hospital treatment for suspected NSO overdose remain prompt identification, airway support, and naloxone administration.[3, 24] While preparing naloxone, first responders and onlookers should get instruction on how to recognise the opioid toxidrome and begin rescue breathing. Intranasal (IN) distribution utilising commercially available 4 mg nasal spray devices is recommended for casual observers; intramuscular (IM) injection (0.4–2 mg) is appropriate for trained first responders.[3]

7.2 Naloxone Dosing Strategy for NSOs

Standard naloxone dosage guidelines for heroin and conventional opioid overdoses are frequently insufficient for NSO reversal. Both the greater potency of fentanyl mimics and the slower receptor dissociation kinetics of nitazenes result in increased naloxone requirements.[3, 6, 24] A scoping examination of nitazene overdose cases found that many high-dose naloxone doses and extended hospital admissions were often documented in clinical case reports (Berger et al., 2025).[3] Emergency physicians should be prepared to administer cumulative naloxone dosages of 4–20 mg when an NSO overdose is suspected, titrating according to clinical response rather than a predetermined ceiling dose.[3, 24]

Naloxone has an elimination half-life of 60 to 90 minutes, which is significantly less than other nitazenes' duration of action. This pharmacokinetic mismatch may cause "renarcotization" in patients who initially respond to naloxone: when naloxone is removed while the NSO is still active at opioid receptors, respiratory depression and coma may return.Therefore, following a confirmed or suspected NSO overdose, all patients who have taken naloxone should be admitted for observation for at least 12 to 24 hours with continuous monitoring [6,33]. Continuous naloxone infusions—roughly two-thirds of the effective reversal dosage per hour—are a recognised strategy for reducing the risk of renarcotization.[2, 3, 36]

7.3 Airway and Ventilatory Management

Supplemental oxygen and bag-valve-mask (BVM) ventilation are first-line airway treatments. When naloxone is unable to provide sufficient reversal, the primary life-sustaining technique is BVM breathing.[2, 36] Endotracheal intubation is indicated in cases of significant aspiration or non-cardiogenic pulmonary oedema, cardiac arrest, wooden chest syndrome that hinders effective BVM breathing, and coma with absent or inadequate respiratory effort that is not responsive to naloxone.[2,4] Specifically, in situations with wooden chest syndrome, rocuronium or succinylcholine may be required to achieve enough relaxation for intubation.[4]

7.4 Intensive Care Management

Patients with severe NSO toxicity may need to be admitted to the intensive care unit in order to manage complications (non-cardiogenic pulmonary oedema, aspiration pneumonia, rhabdomyolysis, acute kidney injury from myoglobinuria), mechanical ventilatory support, haemodynamic monitoring, and prolonged naloxone infusion therapy.[2,3] Patients who overdose on nitazene seem to spend a lot more time in the intensive care unit because nitazene poisoning lasts longer than equivalent heroin overdoses.[3, 20]

7.5 Treatment of Opioid Use Disorder and Harm Reduction

A non-fatal NSO overdose presents a critical opportunity for opioid use disorder (OUD) treatment in addition to being a medical emergency. Opioid use disorder (MOUD) medication should be started during the index hospital stay, according to strong evidence.[35] Methadone and buprenorphine continue to be the gold standards for treating OUD.[38] When administering buprenorphine to patients with NSO dependent, therapeutic care is required to manage the risk of precipitated withdrawal, which can occur if high-affinity full agonists are still connected to opioid receptors. Low-dose induction methods and "microdosing" buprenorphine regimens have been observed to lessen this risk.[18, 35]

A take-home naloxone kit with information on how to use it appropriately and the importance of never using it alone should be given to every patient who survives an NSO overdose.[36] There is strong evidence that providing naloxone to drug users' (PWUD) peers and household connections lowers the number of overdose deaths.[14, 40]

Table 4 provides a step-by-step clinical management algorithm.

Table 4. Clinical Management Algorithm for Suspected NSO Overdose

Phase	Intervention	Considerations for NSOs
Immediate (0–5 min)	Call emergency services; position patient; BLS/CPR if pulseless	Do not delay CPR; NSO overdoses often present in cardiac arrest
Naloxone Administration	Initial: Naloxone 0.4–2 mg IV/IM/IN; repeat every 2–3	Expect higher doses; nitazenes may require 4–20 mg total;

	min; up to 10–20 mg cumulative	monitor for rebound toxicity due to shorter naloxone half-life
Airway Management	Supplemental O2; bag-valve-mask; endotracheal intubation if necessary	Wooden chest syndrome may complicate intubation; consider neuromuscular blockade if severe rigidity
Monitoring	Continuous pulse oximetry, ECG, capnography, serial neurological assessments	Extended observation (minimum 12–24 h); watch for renarcotisation
ICU / Hospital Admission	Indicated for coma, cardiac arrest, refractory hypoxemia, recurrent respiratory depression	High threshold for ICU; mechanically ventilate if needed; naloxone infusion may be required
Toxicology Workup	Blood, urine, and gastric samples; LC-MS/MS confirmation	Standard immunoassay will be negative; request targeted NSO panel; inform lab of clinical suspicion
Harm Reduction / Follow-up	OUD assessment; MOUD referral; naloxone prescription for patient and associates	High mortality after non-fatal overdose; ensure linkage to OUD treatment; prescribe take-home naloxone kit

8. FORENSIC TOXICOLOGY AND POST – MORTEM CONSIDERATIONS

8.1 Post-Mortem Toxicology in NSO-Related Death

The post-mortem toxicological analysis of NSO-related mortality is further complicated by the absence of routine screening panels that include these compounds.[1, 8] The extreme mortality of the class is demonstrated by the fact that 82% of nitazene toxicological cases reported between 2019 and 2024 were post-mortem cases, according to UNODC monitoring records. In many nations, these deaths are first categorised as "cause undetermined" or "mixed drug toxicity" when normal toxicology is unable to define the causative agent. [8,9]

Post-mortem redistribution (PMR) is the process by which lipophilic medications move from tissue storage into central blood compartments after death. This can lead to central blood drug concentrations that are many times higher than antemortem peripheral blood concentrations.[11,26] Vitreous humour and peripheral blood (femoral vein) are suggested matrices for post-mortem quantitative assessment of NSOs because they are less vulnerable to PMR.[11]

8.2 Medico-Legal Implications

When customers are unaware of the NSO contamination of the pharmaceuticals they take—a common scenario given the adulteration of heroin, counterfeit oxycodone pills, and other opiates with nitazenes—the concept of informed consent to the specific pharmacological risk is significantly jeopardised. [19,37] Criminalising drug supply as a public

health strategy generates ethically questionable difficulties when drug suppliers are prosecuted in NSO-related deaths in jurisdictions with drug-induced homicide statutes.[19]

9. PUBLIC HEALTH CHALLENGES

9.1 Epidemiology and Surveillance

Accurate epidemiological description of the NSO pandemic is hampered by the same diagnostic limitations that impede therapeutic treatment.[30,33] Between 2020 and 2021, at least 200 overdose deaths in North America and Europe are believed to have been caused by nitazenes; these figures are considered to be substantial undercounts.[9,37] The UK recorded 179 nitazene-related deaths between June 2023 and May 2024, signifying a public health emergency.[20]

The Estonian case study is a cautionary tale. Since 2022, nitazenes have swiftly surpassed fentanyl as Estonia's most prevalent illicit opioid.[20] Drug-related deaths more than quadrupled from 39 in 2021 to 80 in 2022 and over 100 in 2023. Nitazenes are increasingly being identified as the causative agent, according to studies on syringe residues and data from seizures.[20]

9.2 The Continuously Evolving Analogue Landscape

Perhaps the biggest problem with NSOs for public health is their structural flexibility. Clandestine chemists can modify the basic structure of nitazenes to produce new analogues that may retain or exceed opioid potency while escaping scheduled categorisation.[1,5] In 2024 alone, the UNODC EWA found six novel nitazene analogues. The pace of analogue emergence has consistently outpaced the time between first synthesis and international scheduling.[8]

The emergence of orphine analogues (cychlorphine, spirochlorphine) after 2024, which was purportedly spurred in part by stricter Chinese limits on nitazene precursors in 2025, is indicative of this adaptive trend.[31,33] As of May 2026, cychlorphine was still mostly undetected by traditional toxicology panels despite being confirmed in 78 fatal overdose cases and discovered in seized drug samples in 10 countries.[31]

9.3 Regulatory and Legislative Challenges

Class-wide analogue scheduling, which entails scheduling a whole structural class based on comparable pharmacological properties, has been studied in both the United States (under the Federal Analogue Act) and the United Kingdom.[19,22] Nevertheless, its implementation is complicated by the difficulty of exactly defining the class's structural scope to capture innovative analogues without inadvertently include legitimate medicinal compounds.[19] The UNODC and the Commission on Narcotic Drugs (CND) have made headway toward the global scheduling of several nitazene analogues, with eleven compounds recognised under international control as of early 2025; nevertheless, this compound-by-compound procedure is inherently reactive.[8,9]

Diplomatic structures like as the US-led Global Coalition to Address Synthetic Drug Threats, which the European Union joined in 2023, demonstrate the development of global institutional competence for supply-side intervention.[34,22] The manufacturing of NSOs is concentrated in a few countries, and China and India have been

identified as the primary manufacturers of nitazene precursors due to geographical restrictions for enforcement cooperation.[19]

9.4 Harm Reduction Strategies

Harm reduction for NSOs requires adaptation of strategies developed for the heroin and fentanyl epidemics. Key components include: [30,37]

- High-dose take-home naloxone distribution: Standard 0.4 mg naloxone kits are inadequate for NSO overdose. Distribution of 4 mg nasal spray devices, along with education on the need for multiple doses and repeat administration, is essential.
- Supervised drug consumption facilities (SCFs): These settings allow drug use under medical supervision, with immediate access to opioid reversal and emergency care, and have demonstrated effectiveness in preventing overdose death and creating MOUD linkage points.
- Drug checking services: Point-of-care mass spectrometry services that allow persons who use drugs to check the content of their supply before use provide valuable epidemiological intelligence on the evolving drug market.
- Never-use-alone programmes and overdose hotlines: Telephone and digital services that can summon emergency services if the caller becomes unresponsive address the high proportion of overdose deaths occurring in isolation.
- Wastewater epidemiology: LC-MS/MS analysis of municipal wastewater can detect NSO presence and approximate community-level prevalence, serving as an early warning system preceding overdose hospitalisation and mortality signals.
- Public awareness campaigns: Community campaigns targeting both people who use drugs and the general public regarding NSO presence, overdose signs, and naloxone administration are critical components of a layered response.

9.5 Healthcare System Preparedness

Emergency departments and first responder systems must be able to recognise NSO overdose and administer high-dose naloxone treatments when a regular UDS is negative.[3,24] Clinical practice guidelines from emergency medicine and toxicology organisations must be revised to reflect the present NSO threat situation, and laboratory facilities must expand their capacity for NSO screening.[3, 33]

Healthcare worker education is a crucial but now underutilised aspect of preparedness.[30] Medical, nursing, pharmacy, and paramedic training programs need to incorporate NSO toxicological knowledge in order to develop a clinical workforce capable of managing the evolving synthetic opioid issue.[30, 34]

10. FUTURE DIRECTIONS AND RESEARCH GAPS

10.1 In Vivo Pharmacokinetic Studies

Nearly majority of the human nitazene toxicokinetic data comes from in vitro systems and forensic post-mortem examinations.[7,13] Although traditional pharmacokinetic studies are prohibited by ethical and legal constraints, observational in vivo studies using minimally invasive sampling in the context of confirmed clinical exposures would provide crucial insights into distribution volumes, half-lives, and pharmacokinetic-pharmacodynamic relationships governing the duration of toxicity.[13, 28]

10.2 Novel Antagonist Strategies

The known limits of naloxone against high-potency, slow-dissociation NSOs have raised interest in next-generation opioid antagonist techniques. Long-acting antagonists, such as naltrexone depot formulations, have the potential to extend MOR blocking, perhaps outlasting nitazene's duration of action.[3,6] Nalmefene, an opioid antagonist with a somewhat longer half-life (around 8–12 hours) than naloxone, has been studied as a replacement or complement in the treatment of high-potency opioid overdoses.[3, 33]

10.3 Point-of-Care Diagnostics

The development and validation of rapid, affordable, and analytically sound point-of-care assays for NSO detection—such as the fentanyl test strips that have achieved widespread harm reduction implementation—is a crucial unmet need.[40, 30] While lateral flow immunoassay technologies, miniaturised mass spectrometers, and aptamer-based sensors are promising approaches, they require thorough validation against the varied analyte landscape of NSOs [30].

10.4 Predictors of Severe Outcomes

The availability of comprehensive clinical registry data that connects NSO exposure, CYP pharmacogenomic profiles, co-substance use, naloxone dosage, and clinical outcomes would enable the development of risk stratification tools to guide management decisions.[7,35] International collaboration between forensic toxicology services, clinical toxicology units, and poison control centers would be required to gather datasets of sufficient scale.[2, 20]

10.5 Harm Reduction Technology and Policy Evaluation

A comprehensive evaluation of the efficacy of NSO-specific harm reduction initiatives requires health economic modelling and outcomes research.[30] Most of the data base is based on extrapolation from the literature on heroin and fentanyl harm reduction, and there is currently limited direct evidence for NSO-specific efficacy.[30, 37, 40]

11. CONCLUSIONS

Emerging synthetic opioids, such as nitazenes and the ever-expanding range of fentanyl analogues and structurally distinct substances, provide a paradigm-shifting challenge to clinical toxicology and global public health.[1, 8, 9] Because of their exceptional potency, structural heterogeneity, diagnostic invisibility to standard immunoassay screens, partial or total resistance to standard naloxone reversal, and potential for rapid analogue innovation, they pose

a threat that exceeds the capacity of the current clinical, laboratory, regulatory, and public health infrastructures to adapt.[5, 6, 19]

The nitazenes in particular provide a mechanistically distinct risk due to their delayed receptor dissociation kinetics, which induce both prolonged toxicity and lower naloxone reversibility.[6,33] The clinical and forensic literature that is currently emerging from case series, in vitro pharmacological studies, and wastewater surveillance presents a consistent picture: these compounds are widely distributed in the illicit drug supply, frequently consumed inadvertently as adulterants, and associated with severe overdose outcomes that require prolonged and resource-intensive medical management.[2, 3, 20, 35]

To effectively handle the NSO scenario, a coordinated, multi-layered strategy is required. This calls for revising overdose management recommendations that take partial naloxone resistance at the clinical level into consideration, as well as extending toxicological testing capabilities and including OUD therapy into every NSO overdose encounter.[3,24,38] At the public health level, it requires significant expenditures in harm reduction infrastructure, monitoring systems that can detect NSOs before death signals, and healthcare staff education.[30,34] At the international and regulatory level, it requires flexible legal frameworks that can respond to analogue innovation faster than the current compound-by-compound scheduling paradigm, as well as continuous multilateral engagement with source and transit countries.[19, 22]

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