Clinical Experiences With the Nitazene Class of Synthetic Opioids: A Cohort Study

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Study objectives: Nitazenes are illicit novel opioid agonists, and data describing the clinical course, management, and outcome of nitazene opioid poisoning are limited. The aim of this study is to describe our clinical experiences with analytically confirmed nitazene opioid exposures.

Methods: We extracted data on analytically confirmed nitazene opioid exposures in a cohort of prospectively identified cases in a state-based comprehensive surveillance program in New South Wales, Australia.

Results: We identified 27 laboratory-confirmed nitazene opioid exposures from June 2018 to March 2025. We observed 20 unintentional acute opioid poisonings and 7 acute withdrawals in predominantly younger men. Protonitazene, protonitazepyne (N-pyrrolidino-protonitazene), and isotonitazene were the most detected nitazene opioid compounds. The most common route of exposure was vaping; other exposures included injection, ingestion, and nasal insufflation. Nitazene opioids were sought in 8/21 (38%) of cases where intent was known. Acute poisoning typically presented with sedation and hypoventilation, necessitating endotracheal intubation in severe cases due to cardiac arrest and/or hypoxemia. Naloxone was effective, with a median parenteral reversal dose of 400 μg (interquartile range 400 to 800 μg) and repeat dosing was given in 45% of the 11/16 cases receiving naloxone.

Conclusion: This case series highlights that standard parenteral naloxone doses are typically effective, but ongoing monitoring is necessary to detect renarcotization. Nitazene opioids display novel consumption patterns, including exposure by vaping and unintentional use in products sold as containing another drug. The risk of opioid withdrawal from regular nitazene opioid use is a novel observation. Monitoring trends through active drug surveillance, public education, and community access to naloxone are crucial to mitigate the harm posed by nitazene opioid opioids. [Ann Emerg Med. 2025;86:475-483.]

Please see page 476 for the Editor's Capsule Summary of this article.

Keywords: Nitazene, Illicit, Novel opioid, Poisoning, Withdrawal.

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INTRODUCTION

Background

Nitazenes are illicit synthetic benzimidazole opioid analogs that pose an emerging concern due to the increasing number of clinical, forensic, and police seizure reports. The United Nations Office on Drugs and Crime Early Warning Advisory on New Psychoactive Substances notes a rapid increase in both unique nitazene opioids and countries where they are detected at a rate exceeding that of fentanyls.[1] Novel psychoactive substances are variably classified but are commonly defined as substances which do not fall under international drug controls, but which may pose a public health threat comparable with substances that are currently prohibited.[2] Although some nitazene opioids (eg, metonitazene and etonitazene) were first described in the 1950s, they were not used in clinical practice so clinical data for these and other recently detected nitazene opioids are extremely limited.[3]

In Europe, benzimidazoles have outnumbered fentanyl analogs since 2020.[4] Recently, nitazene opioids are more commonly encountered than illicit fentanyl and analogs in Australia, and the subject of multiple drug warnings and deaths.[4-7] In the United States, nitazene opioids are a public health concern with nearly 7,000 reports to the US Drug Enforcement Agency's National Forensic Laboratory Information System between 2019 and March 2025.[8]

Editor's Capsule Summary

What is already known on this topic

Nitazenes are illicit newer opioid agonists with health consequences.

What question this study addressed

What is the clinical experience with confirmed nitazene opioid exposures in an Australian state-based comprehensive surveillance program?

What this study adds to our knowledge

Vaping was the most common route of exposure; symptoms were typical of opioid exposure and responded to naloxone with a median dose of 400 mcg. Repeat naloxone administration was often needed.

How this might change clinical practice

Nitazene toxicity responds to naloxone. Nitazene withdrawal similar to traditional opiods occurs.

Importance

Data describing the clinical course and outcome of nitazene opioid poisoning are limited. The more than 40 nitazene opioids vary in potency (usually exceeding heroin), effect, and probably half-life, which will affect the dose of naloxone that reverses respiratory depression without precipitating withdrawal and the subsequent minimum duration of monitoring.[9-12] A recent review noted median total naloxone doses 1 to 6 mg, but that the minimum effective dose was not known.[13]

A US study reporting 7 cases noted a nonsignificantly lower mean total naloxone dose of 4.4 mg for benzimidazoles (7 nitazene and 2 brorphine cases), compared with 6.41 mg for fentanyl poisonings. Benzimidazole overdoses typically received more than or equal to 2 naloxone doses, whereas fentanyl overdoses typically received 1 dose. However, sedative coexposures were common.[14] A UK study reported 20 cases involving N-desethyl isotonitazene, with similarly high incidence of sedative coexposures. Naloxone was administered to 70% of cases, median dose 800 μg out-of-hospital; 7 (50%) received further doses in hospital, and 5 received a naloxone infusion.[15] An Australian study described 32 presentations with mostly unintentional nitazene opioid use, in whom naloxone was administered to 72% (median dose 400 μg and 4 received a naloxone infusion) and 32% were intubated; 97% of presentations had coexposures, mostly with methamphetamine.[16]

Additional clinical data about nitazene opioid poisoning are necessary to guide management, including naloxone dosing and subsequent monitoring.[17] Differences between individual nitazene opioids are also of interest.

Goals of This Investigation

We describe characteristics of nitazene opioid exposures identified by a state-wide illicit drug monitoring program that prospectively records clinical and laboratory data in patients with severe and unusual substance-related toxicity. The clinical presentations, management, and outcome of acute nitazene opioid poisoning are described.

METHODS

Study Design and Setting

We extracted data from the Prescription, Recreational and Illicit Substance Evaluation (PRISE) Program database, managed by New South Wales Ministry of Health in Australia. PRISE is a clinical and public health program that provides access to extensive toxicology testing at New South Wales Health acute care services.[18] Cases are identified through a prospective comprehensive surveillance program that includes referrals from clinical services (clinical toxicology, Poisons Centre, paramedics, alcohol, and other drug services), active case finding from emergency presentations, and notifications from forensic clinical and laboratory services. PRISE criteria include severe and unusual harm or clusters relating to suspected substance use or emerging substances of concern (nitazene opioids are specifically targeted). This includes patients who are intubated, admitted to intensive care, or who require multiple doses of naloxone or a naloxone infusion, or specifically report using novel opioids.[18] Patients are mostly referred while critically unwell in the emergency department (ED) or ICU.

This database comprises a minimum data set of demographics and clinical and laboratory details recorded by trained clinicians at the time of referral. Each referral is followed until discharge or death to ensure complete data capture. The PRISE database also includes clinical and coronial toxicology samples analyzed by the Forensic Toxicology laboratory of the Forensic & Analytical Science Service of New South Wales Health Pathology and drug samples analyzed by the Illicit Drug Analysis Unit laboratory of Forensic & Analytical Science Service.

Blood, urine, and/or drug substances undergo extended toxicological analysis using chromatography and mass spectrometry. Data independent acquisition (a method for characterizing a drug structure by fragmenting the parent molecule into smaller ions that are then characterized using mass spectrometry) results are compared with in-house and international high-resolution mass spectral databases containing more than 5,000 toxicologically relevant drugs and poisons. Postrun processing of data compares accurate mass

measurements with known molecular and product ions. These data are supplemented with immunoassay urine drug screens.

Selection of Participants

Nitazene opioids are a prespecified category within the PRISE database. We extracted clinical and laboratory data (see Appendix E1, available at http://www.annemergmed.com, for details) for all cases of laboratory-confirmed nitazene opioid exposure between July 1, 2018, and March 31, 2025, into a purpose-built spreadsheet. Additionally, a back-up search for "nita" was performed to identify possible miscoding.

Interventions

This is a noninterventional observational cohort study.

Measurements

A spreadsheet for the purposes of this study was constructed. Most of the data fields were identical to the minimum data set for the prospective PRISE clinical database, and some other fields were added, as detailed in Appendix E1. These extra data and data missing from the PRISE clinical database (if any) were extracted from the electronic medical record of the hospital treating the patient by 2 trained medical doctors employed by the PRISE program with expertise in acute medicine (including critical care and clinical toxicology) for use in this report. A minimum of 20% of cases were independently extracted by both medical doctors to assess for potential interrater differences which was graded using the kappa statistic. Both extractors were broadly familiar with the rationale of the activity because it aligns to the overall goals of the PRISE program, but they were not informed of the specific hypotheses. Nevertheless, all data being extracted were discrete or continuous data that are reported in the hospital electronic medical record as part of standard clinical care, in contrast to qualitative data that can be subject to interindividual differences in interpretation. Further details of the methodology of the retrospective component of this study are detailed in Appendix E1.

Outcomes

We describe the demographics, details of substance use, presenting clinical features, treatments, and outcomes including survival and complications. Hypoventilation was defined as respiratory rate less than 8 breaths per min, or unquantitated bradypnea that resolved with naloxone. Miosis was defined as pupil diameter of less than or equal to 2 mm. The dose of naloxone that the treating clinician administered for reversal of nitazene opioid poisoning, particularly hypoventilation, was considered the "reversal dose." We also describe results of laboratory investigations including detailed toxicology testing.

Analysis

We conducted a frequency evaluation of cases involving nitazene opioids and their clinical characteristics. Categoric variables were expressed as counts and percentages, whereas continuous data were expressed as median and interquartile range (IQR); the range of demographics was not reported due to the small number of cases.

Ethics

PRISE is a state-wide clinical and public health program. It provides access to extensive toxicology testing to New South Wales Health acute care services for cases of severe and unusual substance-related toxicity or clusters of overdoses for clinical and public health purposes, with rapid turnaround time. This is a quality improvement or quality assurance activity and in accordance with New South Wales Health Guideline GL2007_020 does not require independent ethics review. Therefore, consent was not required for reporting these deidentified data. Furthermore, the decision to report these cases occurred when the assay results returned which was after patients had been discharged from hospital. The New South Wales Population and Health Services Research Ethics Committee confirmed that this report does not raise ethical risks requiring submission to an ethical review body (reference EFF/25/25360).

RESULTS

Of 1,488 cases referred to PRISE between July 1, 2018, and March 31, 2025, 1,014 cases were tested, 854 have finalized results, and 27 were laboratory-confirmed nitazene opioid exposures (Figure). The first confirmed case was in April 2021 with a steady rise afterward.

There was a high level of agreement between the 2 extractors (Kappa statistic 0.96) with the most common point of difference relating to the documentation of miosis in the hospital medical record.

Characteristics of the Study Subjects

Overall, 23 analytically confirmed hospital presentations were referred to PRISE by clinicians and 4 cases were identified in coronial forensic investigations. Cases were mostly younger (median age 26 years, IQR 22 to 31 years) and men (23/27, 85%). Cases were subclassified as acute opioid poisoning (20/27 (74%) and acute opioid withdrawal from chronic nitazene opioid vaping in 7/27 cases (26%) (Figure).

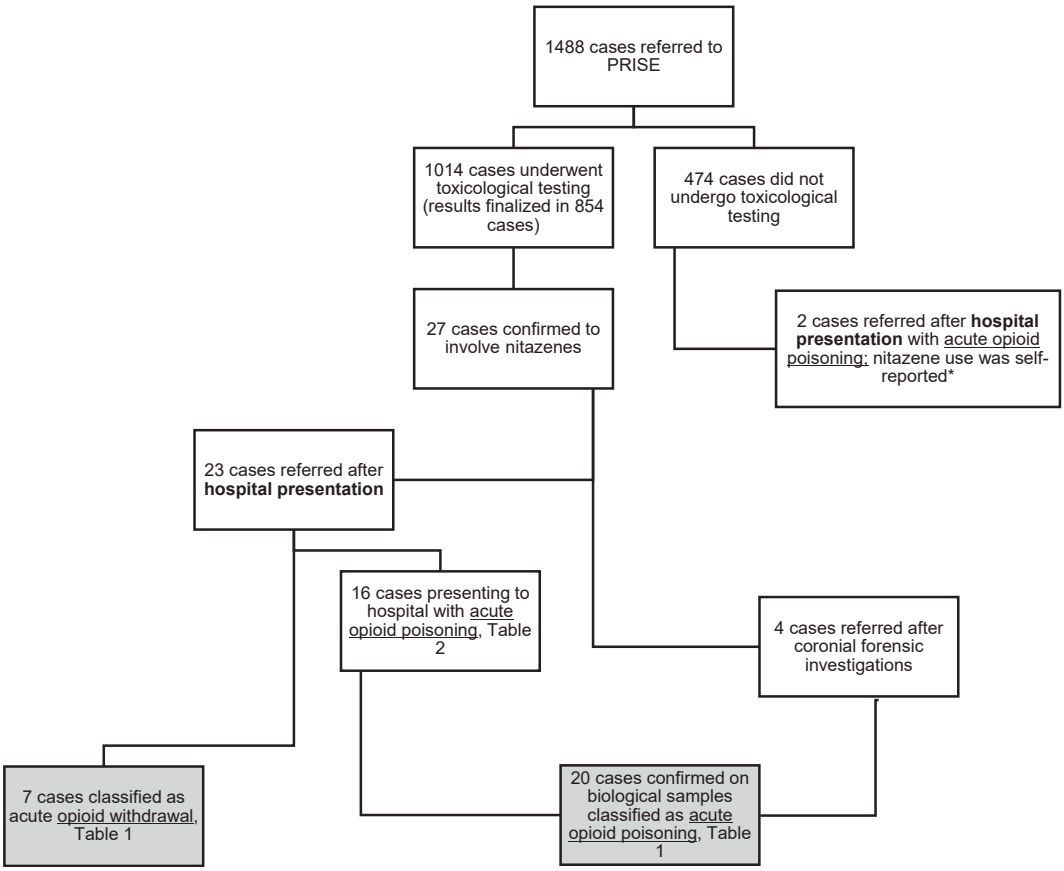

Figure. Summary of the identification and classification of nitazene opioid exposures in the PRISE database. Gray-colored boxes indicate demographic and clinical data reported in formal analysis. *Not included in formal data analysis due to nonconfirmed nitazene opioid use.

Two cases with acute opioid poisoning self-reported nitazene opioid use and no samples were available for laboratory testing so are briefly described here but not otherwise considered further. One case of vaping developed cardiorespiratory arrest and ventricular tachycardia managed with cardiopulmonary resuscitation and recovered. The other case involved nasal insufflation after ingestion of alprazolam, resulting in mild drowsiness with normal respiratory function.

The demographics and substance use characteristics of the 27 cases with laboratory-confirmed nitazene opioid exposures are summarized in Table 1. Laboratory confirmation was mostly based on blood testing in cases with acute opioid poisoning, and substance testing in cases with acute opioid withdrawal. The blood samples tested were mostly from the time of admission, whereas urine samples were often collected hours (and sometimes days) later. Six nitazene opioids were detected, the most common being protonitazene in 11/28 (39%) of all cases (Table 1). Concordant results were noted in 8/11 (73%) of acute cases and 3/3 (100%) of withdrawal cases in whom both blood and urine samples were available for testing. The discordant results were noted in 1 case of protonitazene (positive urine and negative blood) and 2 cases of isotonitazene (negative urine and positive blood). A range of routes of exposure were noted, most commonly vaping (through refillable e-cigarette devices using refill liquid) in 11/27 cases (41% overall; but in 100% of acute opioid withdrawal cases) followed by ingestion and injection in 5/27 (19%) each (Table 1). Nitazene opioids were not specifically sought in 13/21 cases (62%) where intent was known, of which nonopioid drugs were sought in 11/13 (85%) of these cases; intent was unknown in 6/27 (22%) (Table 1). Sedative coconsumption was reported in only 7/23 (30%) hospital presentations, but 18/20 acute poisonings with biological samples were positive for codetections (Table 1). The 2/20 without codetections tested positive for protonitazepyne (N-pyrrolidino-protonitazene; both intended to take 3,4-methylenedioxymethamphetamine; MDMA).

Table 1. Demographics and characteristics of cases with laboratory-confirmed nitazene opioid use.

Demographics	Acute Poisoning (n=20)	Opioid Withdrawal (n=7)
Age (y)	Median 27 (IQR 24-33)	Median 22 (IQR 21-24)
Sex	Men, n=16	Men n=7
	Women, n=4	
Route of exposure		
Vaped (inhaled by mouth)	4 (20%)	7 (100%)
Injected	5 (25%)	
Nasal insufflation	3 (15%)	
Ingested	5 (25%)	
Unknown	3 (15%; coronial cases)	
Concurrent exposures*		
Cannabis	2	2
MDMA	3	
GHB	1	
Ketamine	1	
Alcohol	2	
Cocaine	1	
Benzodiazepine	1	
Amphetamines†	3	3
Opioid	1 (heroin)¶	1 (tapentadol)
Nitazene opioid purposely sought		
Yes	6 (30%)	2 (29%)
No	8 (40%)	5 (71%)
	Oxycodone n=2	Cannabis n=5
	MDMA n=3	
	Ketamine or cocaine n=1	
	Synthetic cannabinoid n=1	
	LSD and "magic mushrooms" n=1	
Unknown	6 (30%; including 4 coronial cases)	
Matrices undergoing laboratory testing, and positivity		
Blood positive	17/19 (89%)	3/3 (100%)
Urine positive	7/11 (64%)	3/5 (60%)
Blood and urine positive	6/11 (55%)	3/3 (100%)
Blood and urine negative‡	2/11 (18%)	
Drug substance positive	4/6 (67%)	6/6 (100%)
Nitazenes identified in laboratory testing		
Etodesnitazene	3	
Metonitazene	2	1
Isotonitazene	4	
Protonitazene	4	6
Protonitazepyne**	5	
Isotonitazepyne$	2	
Other drugs found on laboratory toxicology screening|	Benzodiazepines (13#) Amphetamines (6†)	Benzodiazepines (4)
	Ketamine (4)	THC (4)
	THC (4)	Cocaine (2)
	Cocaine (2)	Amphetamines (1†)
	Morphine (3)	Buprenorphine (2)
	GHB (2)	
	Sedating antihistamines (2)	
	Fentanyl (2)	
	Quetiapine (1)	
	MDMA (1)	
	Droperidol (1)	
	Olanzapine (1)	
	Oxycodone (1)	
	Methadone (2)	
	Pregabalin (1)	

GHB, γ-hydroxybutyrate; *LSD*, lysergic acid diethylamide; *THC*, tetrahydrocannabinol; *MDMA*, 3,4-methylenedioxymethamphetamine.
*Excluding the 4 coronial cases.
†Amphetamine or methamphetamine.
‡Nitazene opioid was confirmed in the testing of substances taken by the patient.
$Also known as N-pyrrolidino-isotonitazene.
|Drugs detected as the parent or metabolite in biological samples, which will include treatments administered in hospital, or substances taken days earlier.
¶Consumed a few hours prior.
#Predominantly diazepam and metabolites (temazepam, oxazepam, and nordiazepam), also bromazolam (4), midazolam (2), and clonazepam (1)
**Also known as N-pyrrolidino-protonitazene.

Main Results

All hospital presentations with acute nitazene opioid poisoning had sedation and most had confirmed hypoventilation (Table 2). A total of 5/16 (31%) cases presenting to hospital with acute opioid poisoning were immediately intubated due to cardiac arrest (2 cases; 1 also

Table 2. Clinical features and treatments administered to 16 cases presenting to hospital with nitazene opioid poisoning.

Presenting Clinical Features	Amount (n=16)
Sedation	16 (100%)
Hypoventilation	15 (94%); respiratory arrest in 2 cases
	Unconfirmed in 1 case receiving intranasal naloxone in the community
Miosis (pupil size ≤2 mm)	
No	5 (31%)
Yes	5 (31%)
Unknown	6 (38%); 1 case received intranasal naloxone in the community, not recorded in 5 cases
Other	
Cardiac arrest	2 (asystole n=1, pulseless electrical activity n=1)
Bystander CPR	2 (in the context of marked sedation)
Ventricular tachycardia	1 (in context of hypoxemia from respiratory arrest)
Aspiration pneumonitis	2 (ECMO required in 1 case[‡])
Mild serotonin toxicity	1 (concomitant MDMA)
Treatments	
Immediate intubation and ventilation	5 (31%)
Naloxone administered*	11 (69%)
Naloxone initial reversal dose (median, IQR, range)[†]	400 μg (IQR 400-800, range 200-1,800 μg)
Additional naloxone[†]	5 cases, including an infusion in 3 cases (1 was because of nitazene opioid self-administration in hospital)
Other	
ECMO	1 (for severe aspiration pneumonitis)[‡]
Outcomes	
Survival	14 (88%)
Complications	
Death	2 (severe brain injury; both presented in cardiac arrest)
Rhabdomyolysis	1 (peak creatine kinase 18,500 U/L)[$]
Hypoxic brain injury with mild cognitive impairment	1[$]
Type 2 non-ST elevated myocardial infarction	1 (also developed aspiration pneumonitis)
Referral to alcohol and other drugs team	
Yes	6
No	8
Unknown	2

ECMO, Extracorporeal membrane oxygenation; *CPR*, cardiopulmonary resuscitation.
*Two cases who were promptly intubated also received naloxone but there was insufficient opportunity to observe a clinical response to naloxone, so these cases are not included in this value.
[†]"Reversal dose" was defined as the dose of naloxone that the treating clinician administered for reversal of nitazene opioid poisoning, such as hypoventilation; naloxone administered parenterally in 10 cases, and intranasally in 1 case (1,800 μg).
[‡]Refers to the same case.
[$]Refers to the same case.

received naloxone) or profound hypoxemia from hypoventilation in 3 cases (with coexistent aspiration in 2 patients; 1 also received naloxone). One case experienced sedation with occasional bradypnea (respiratory rate 6 breaths/min) but was easily awakened and did not receive naloxone. Naloxone was administered to 11/16 (69%) of cases of acute opioid poisoning presenting to hospital, specifically parenteral naloxone by health care workers to 10/11 (91%) for unconsciousness (unresponsive to voice) and bradypnea, and intranasal naloxone in 1/11 (9%) by a community bystander for unconsciousness. The median reversal dose was 400 μg and repeat doses were given to 5/11 cases (45% of those receiving naloxone who were not immediately intubated) due to recurrence of sedation and

hypoventilation: 400 μg after 4 hours in a case using etodesnitazene, 400 μg after 30 minutes for a case using protonitazepyne (N-pyrrolidino-protonitazene), naloxone infusion after 45 minutes that continued for 6 hours without dose titration in a case using isotonitazene, and naloxone infusion after 45 minutes that continued for 9 hours (overnight) without dose titration for a case of isolated protonitazepyne. One case using protonitazepyne in whom nitazene readministration during hospitalization was suspected was given 400 μg after 7 hours and then a naloxone infusion was commenced that continued for 11 hours without dose titration.

Overall, complications of those presenting with acute opioid overdose are consistent with delayed presentations and summarized in Table 2. The 2 deaths in hospital presented with cardiac arrest and severe hypoxemia, and despite the return of spontaneous circulation suffered severe hypoxic brain injury.

LIMITATIONS

Limitations include reliance on referrals which may bias to more severe presentations, and likely underestimates the number of cases in New South Wales, some retrospective data extraction in many cases, inability to quantitate nitazene opioid concentrations, and potential confounding of drugs detected in urine tests which could have related to treatments administered or substances taken days earlier.

DISCUSSION

We observed acute opioid poisoning and opioid withdrawal with illicit substance use in a predominantly younger men population. Nitazene opioids were used both intentionally and unintentionally and consumed by multiple routes, particularly vaping of a liquid in refillable e-cigarette devices. The clinical effects and complications of acute nitazene poisoning were consistent with those of opioids and potentially severe, reinforcing the necessity for active drug surveillance programs, public education, and naloxone use in the community to minimize harm.

Nitazene opioids entered the international drug market in 2019, and the annual number of cases has steadily increased.[1] Data on epidemiology are limited, and early data were confined to forensic investigations or case reports.[19] Recent US, UK, and Australian case series did not describe the route of nitazene administration, but we observed nitazene administration by various routes, predominantly vaping (11/27, 41%; Table 1) which appears to be a novel observation.[14,15]

In 38% of our cases (8/21; data unavailable in 6 cases, Table 1), nitazene opioids were sought, and in 11/21 (52%, data unavailable in 6 cases, Table 1) nonopioid substances were sought, compared with 16% and 46% of cases in the recent Australian study.[16] These events prompted New South Wales Health to issue public drug warnings and clinical safety advisories, such as after multiple cases of significant harm occurred when individuals took tablets they believed to be MDMA but contained nitazenes.[20] Nitazene opioid poisonings occurred when vaping a product sold as cannabinoids in another Australian state[21] while we also observed cases of opioid withdrawal from vaping substances sold as cannabinoids that contained nitazene opioids (Table 1). This underscores the importance of public health messaging about risks of opioid poisoning in populations who are not otherwise considered at risk, similar to concerns with opioids being present in substances sold as cocaine or methamphetamine.[22,23] The need for collaboration and sharing of observations in real time is critical with early warning networks and New South Wales actively participates in the Prompt Response Network and United Nations Office on Drugs and Crime Early Warning Advisory.

Nitazene opioids caused a typical opioid toxidrome in our case series, like findings from the US, UK, and Australian series.[14-16] The US study reported higher initial doses of naloxone (mean initial dose 4.13 mg, SD 3.34 mg, intranasal administration in 5/9 cases) compared with the UK study (median 800 μg, range 400 to 2,000 μg, parenteral administration) and the Australian study (depending on the setting, median 400 to 800 μg, range 100 to 1,600 μg, parenteral administration).[14-16] The median initial naloxone dose in our study was less than the US and UK studies, but similar to the Australian study. Similar to these other studies, additional doses of naloxone were required in some cases in our series (Table 2).

Polydrug use was common in our series, like observations in the US, UK, and Australian series (Table 1). Only one case appeared to have an isolated N-desethyl isotonitazene overdose based on a urine sample collected 6 hours after presenting to the ED (personal communication, Dr. Pucci), and he received naloxone 1.2 mg out-of-hospital then 600 μg/h for 10 hours.[10] One case in the Australian study had an isolated nitazene opioid poisoning but other information is not provided.[16] One case of isolated protonitazepyne poisoning in our series received naloxone for 9 hours but dosing was not titrated so a shorter duration may have been acceptable.

Differences in naloxone dosages between patients and studies may be due to various factors. The higher dose in the

United States may be from using intranasal naloxone, which was not reported in the UK, and was uncommon in our study and the other Australian study.[14-16] The US and UK studies had higher proportions of sedative coingestions (including opioids) compared with our study. The dose and specific type of nitazene opioid involved may contribute; N-piperidinyl etonitazene and N-desethyl isotonitazene were not in our study; however, metonitazene and isotonitazene were detected in our study and the US study.[14,15] Protonitazene was the most common nitazene opioid in both Australian studies but not reported in the US or UK studies.

Our study identified 7 cases of opioid dependence from vaping of nitazene opioids several times daily which is a novel observation.

The results of the US and Australian studies support bystander intranasal naloxone for people who may use nitazene opioids.[14,16] Intranasal naloxone was used in only 2 cases in our series (and it reversed opioid poisoning) and was not reported in the UK series.[15]

Strengths of our study include prospective case detection and comprehensive clinical data collection, laboratory confirmation, and complete access to electronic medical records. Few cases had detectable coexposures such as opioids that would substantially affect the clinical presentation and response to naloxone.

In summary, our data offer guidance on the adverse effects profile and management of acute poisonings with nitazene opioids. Standard naloxone doses are typically effective, but ongoing monitoring is necessary to detect renarcotization. Early warning systems to monitor trends in novel opioids like nitazenes and inform harm reduction activities, including using intranasal naloxone and medical review because of the risk of renarcotization, remain crucial. This is of interest to at-risk individuals and health care workers.

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Author contributions: DR, BT, JB conceptualized and designed the study. JB, TJ, CH, MS, BT designed and/or maintain the cohort study. BT, JB, MS, CH obtained the data. DR, BT, MS conducted the statistical analysis. DR drafted the manuscript. All authors reviewed the manuscript and made substantial contributions and approve the final version. DR takes responsibility for the manuscript as a whole.

Data sharing statement: Due to ethical restrictions, the data that support the findings of this study may be available upon reasonable request from the corresponding author.

All authors attest to meeting the four ICMJE.org authorship criteria: (1) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND (2) Drafting the work or revising it critically for important intellectual content; AND (3) Final approval of the version to be published; AND (4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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