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Understanding emerging high potency opioids: effects and naloxone dosing

Suzanne Nielsen BPharm BPharmSc(Hons) PhD MPS
Professor and Deputy Director, Monash Addiction Research Centre

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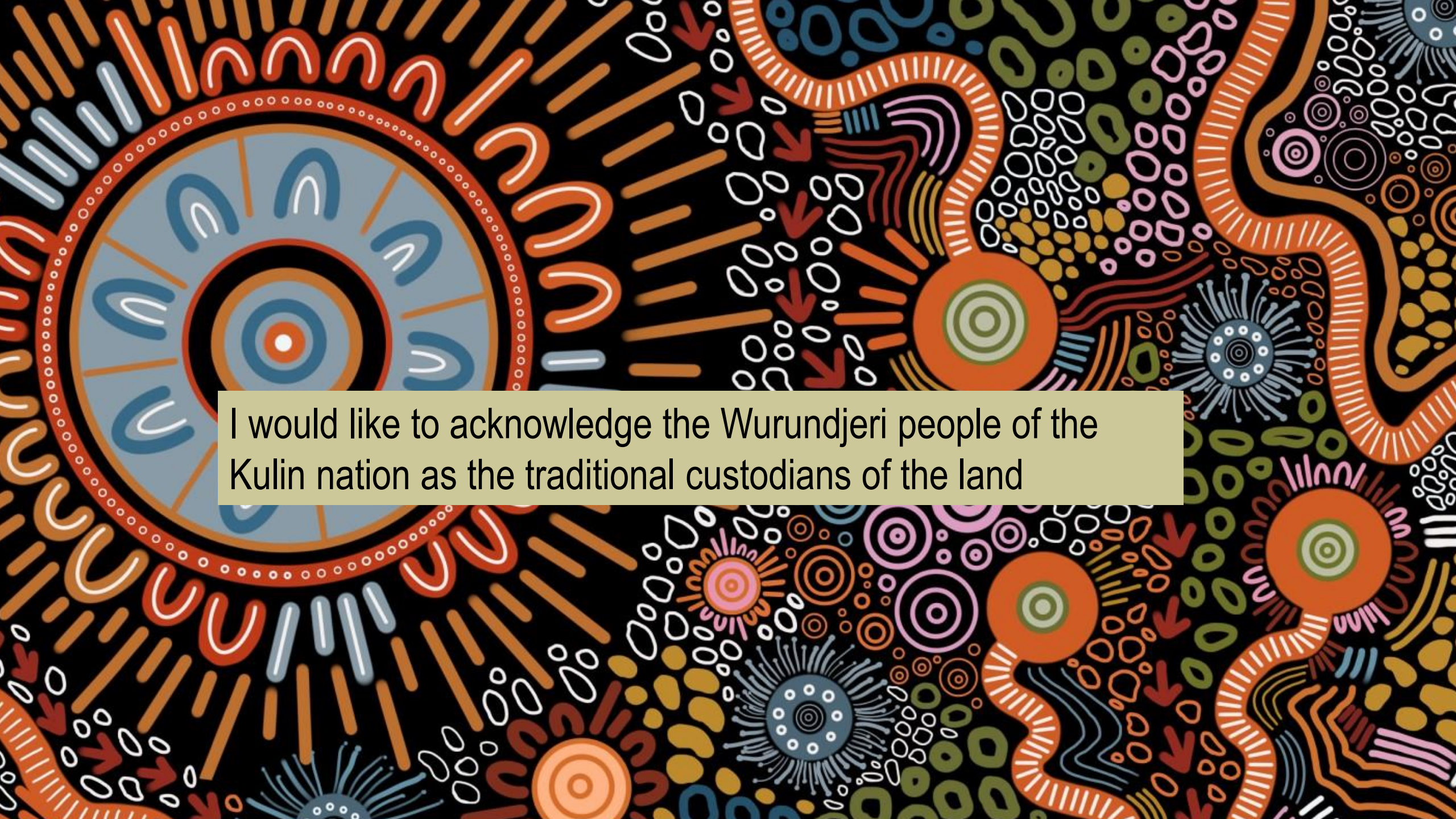
VAADA conference

DrSuziNielsen

linkedin.com/in/suzanne-nielsen


I would like to acknowledge the Wurundjeri people of the Kulin nation as the traditional custodians of the land

Global emergence of potent synthetic opioids

- **2015:** Fentanyl and analogues (e.g., acetylfentanyl) emerged in North America and parts of Europe, but uncommon in most of Europe, the UK, and Australia
- **Regulatory Response:** From 2015, recommendations were made for international controls of different fentanyl analogues, fentanyl analog legislation (e.g., USA, China) was introduced
- **Newer Synthetic Opioids:** around 2019 benzimidazole opioids (e.g., brorphine) and nitazenes (e.g., isotonitazene, metonitazene) emerged

What are nitazenes?

- Synthetic opioids, with similar analgesic, respiratory, sedative and dependence liability to other opioids, some more potent
- Structurally distinct from fentanyl and other opioids to date
- Explored for medical use in the 1950s but abandoned due to side effect profile

Increasing alerts: Nitazenes in Australia

- Increasing detections and harm from synthetic opioids across Australia (first detected 2021)
- Appearing as contaminants (likely unintended) in stimulants like cocaine (4 deaths in Broadmeadows, 2023), MDMA, ketamine, as well as in heroin and falsified pharmaceutical pills

9NEWS

News / National

Four people found dead in Melbourne home had 'synthetic opioid' in system

By Adam Vidler, Emily Bennett | 12:32pm Jul 4, 2024

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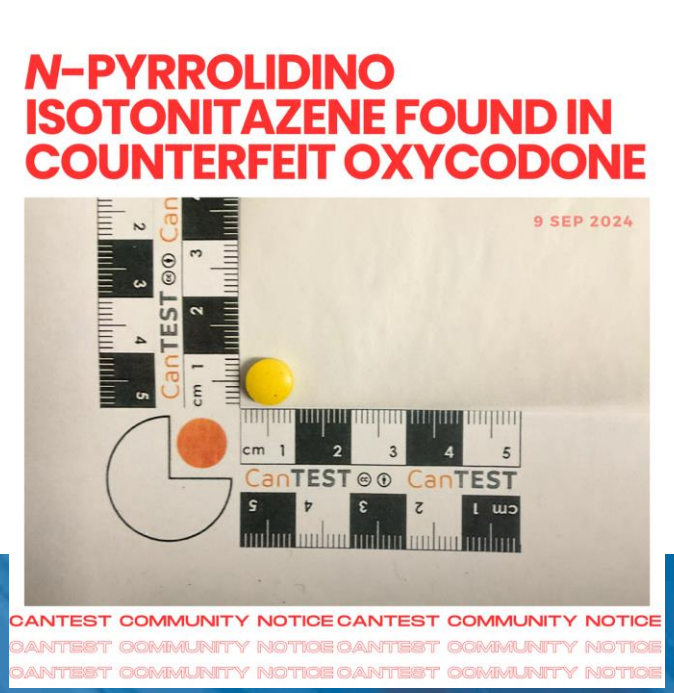
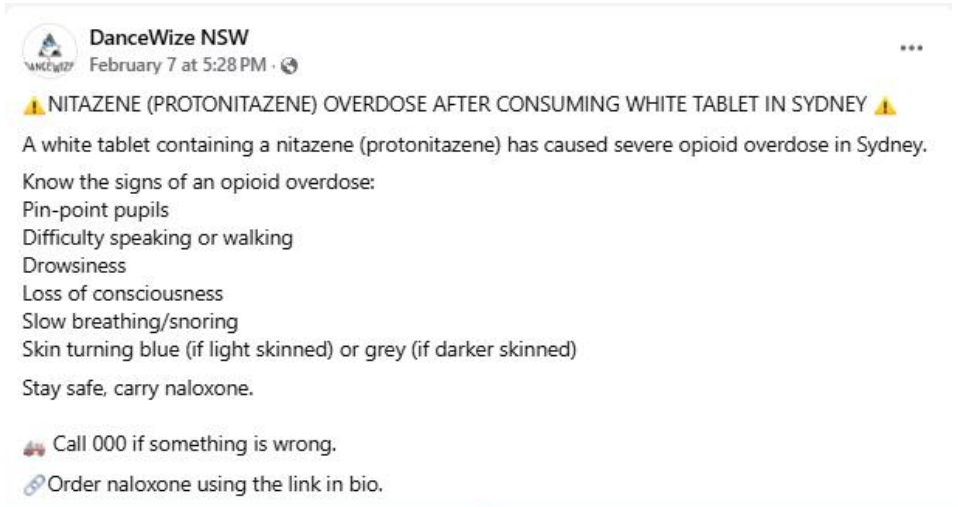
Early tests have confirmed the presence of a synthetic opioid in the system of four people who were found dead in a Melbourne home last week.

Four bodies, of a 32-year-old man, a 37-year-old man, a 42-year-old woman, and a 17-year-old boy, were found in a Bicknell Court home in Broadmeadows at about 2am on June 25.

Police have now said a "synthetic opioid" was found in the systems of all four.

READ MORE: Biden privately acknowledges next days are critical to save reelection bid





DanceWize NSW
February 7 at 5:28 PM ·

⚠️ NITAZENE (PROTONITAZENE) OVERDOSE AFTER CONSUMING WHITE TABLET IN SYDNEY ⚠️

A white tablet containing a nitazene (protonitazene) has caused severe opioid overdose in Sydney.

Know the signs of an opioid overdose:
Pin-point pupils
Difficulty speaking or walking
Drowsiness
Loss of consciousness
Slow breathing/snoring
Skin turning blue (if light skinned) or grey (if darker skinned)

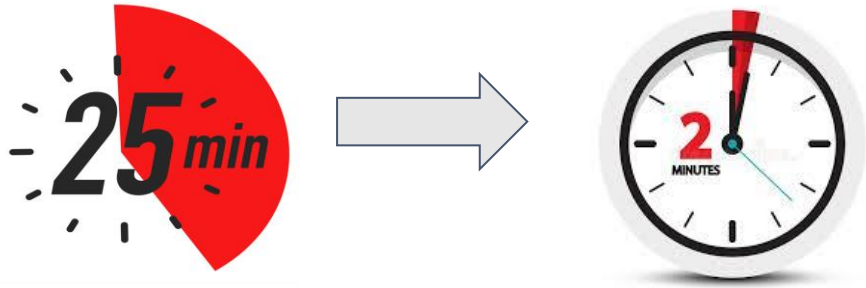
Stay safe, carry naloxone.

🚑 Call 000 if something is wrong.

🔗 Order naloxone using the link in bio.

Pharmacology and potency of nitazenes

- Nitazenes bind strongly to the μ-opioid receptor, often with high potency → risk of sudden, profound respiratory depression



- Some (but *not* all) nitazenes exceed fentanyl's effects (e.g. by 10-12 times), some weaker

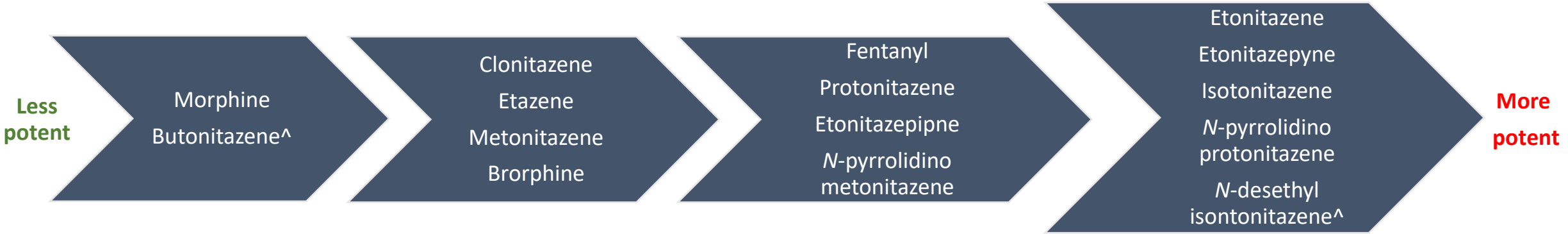


Figure: Approximate rank order potency based on behavioural studies (antinociceptive assays); ^potency estimate can vary with assay type

Profile of key nitazenes: early nitazenes explored for clinical use

Clonitazene and etonitazene tested as part of a series of nitazene compounds in the 1950s, abandoned after early clinical trials

Only two controlled in the original 1961 convention:

- **Clonitazene**: used in early clinical trials (1950s, 300 patients) → does not appear to cause respiratory depression even though more potent than morphine (between morphine and fentanyl in potency)
- **Etonitazene**: One of the most potent (10-12 x that of fentanyl, 1000x that of morphine), use not widespread but has been found in falsified oxycodone products. Fast onset of action and produces muscle rigidity (reminiscent of 'wooden chest syndrome') in rats.

NPS nitazenes

- **Isotonitazene:** Emerged in 2019, frequently detected in North America. ≈3x as potent as fentanyl. Used intentionally (e.g. sold in a multidose intranasal isotonitazene spray), in addition to as a contaminant in other drugs
- **Protonitazene:** Identified in 2020, similar potency to fentanyl, responsible for a cluster of 4 deaths in Victoria in contaminated cocaine, detected in methamphetamine in Adelaide, 3C-P in Melbourne
- **N-pyrrolidino protonitazene (protonitazepyne):** identified in 2022, more potent than fentanyl, most use unintentional (sold as heroin or fentanyl), found in falsified oxycodone in Australia. Responsible for one of the largest overdose clusters documented (sold as heroin), confirmed in 57 cases in Dublin and 20 cases in Cork, Ireland, between November and December 2023

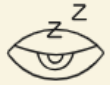
A HSE warning sign in College Green in Dublin. File Picture: Leah Farrell/© RollingNews.ie

Clinical Manifestations of Nitazene Overdose

Symptoms consistent with opioid overdose: deep sedation, pinpoint pupils, and respiratory depression (some cases of prolonged respiratory depression requiring naloxone infusion)

→ Critical to raise awareness among people who use any unregulated drugs about unexpected sedation, drowsiness to think about potential opioid contamination

Many nitazenes short acting, metabolize quickly, and are present in very low doses making clinical and drug checking detection difficult



Extreme drowsiness. Someone has slurred speech, is very hard to wake up (like a deep sleep), or is not responsive or slumped over.

A blue tinge on lips and/or nails with lighter skin or greyish/ashen colour with darker skin.

Someone struggling to breathe, or if they are snoring or gurgling.

The eyes have pinpoint pupils.

The skin is cold and clammy to the touch.

Does naloxone reverse nitazene overdoses?

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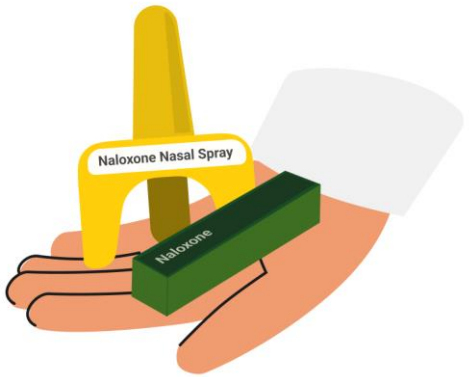
Substance (red = more potent than fentanyl)	Year identified	Naloxone response (Therapeutic dose 0.4mg to 2-8mg)
Etonitazene	1950s	Effective in preclinical studies
Clonitazene	1950s	No respiratory depression was with clonitiazene
Isotonitazene	2019	Case reports of reversal at usual therapeutic doses, one case required infusion
Brorphine	2018	Naloxone blocked respiratory depression on lab studies. Case studies of reversal with usual therapeutic doses.
Metonitazene	2019	0.4mg reversed respiratory depression in two cases, and higher doses in a third, though additional dosing was required, one patient died despite 6mg**(discussed on next slide) During preclinical & early clinical trials, **effects reversed by nalorphine (opioid antagonist <u>less effective than naloxone</u>)**
Protonitazene	2020	Case reports of response to usual therapeutic doses
Etazene (Etodesnitazene)	2020	Naloxone fully reversed nonfatal etazene overdose
Etonitazepyne (N-pyrrolidino etonitazene)	2021	Case report of naloxone reversal (no dose described)
Butonitazene	2019	Case report of reversal at usual therapeutic dose
Etonitazepipne (N-piperidinyl etonitazene)	2021	Case reports (n = 3) of reversal at usual therapeutic doses
N-desethyl isotonitazene	2022	Case report of reversal at usual therapeutic dose. Preclinical evidence also supports naloxone reversal of pharmacologic effects.
N-pyrrolidino protonitazene (protonitazepyne)	2022	Case report of reversal at usual therapeutic dose (n = 2)
N-pyrrolidino metonitazene (metonitazepyne)	2023	No descriptions of naloxone use were found.

What about when naloxone doesn't work

- Naloxone remains the first line of defense
- Many nitazenes very lipophilic (fat soluble) → cross the blood brain barrier very easily and quickly to have a rapid onset
- Naloxone can't work if it isn't administered soon enough, or it isn't available



What about other overdose reversal products?

- **Higher dose naloxone?** Standard dosing sufficient, higher doses associated with greater withdrawal
- **Nalmefene?** Longer duration of action of nalmefene (lasts for around 8h compared to 1h with naloxone → lengthier period of precipitated opioid withdrawal.
- Very limited safety data or clinical experience with nalmefene, and none in with current drugs like novel synthetic opioids

American College of Medical Toxicology and the American Academy of Clinical Toxicology position statement: ***Nalmefene should not replace naloxone as the primary opioid antidote at this time*** (Stolbach et al DOI: 10.1080/15563650.2023.2283391)

Lemen et al. Harm Reduction Journal (2024) 21:93
https://doi.org/10.1186/s12954-024-00994-z

Harm Reduction Journal

REVIEW Open Access

High-dose naloxone formulations are not as essential as we thought

Paige M. Lemen[1,2*], Daniel P. Garrett[1], Erin Thompson[3], Megan Aho[3], Christina Vasquez[3,4] and Ju Nyeong Park[3,4]

Abstract

Naloxone is an effective FDA-approved opioid antagonist for reversing opioid overdoses. Naloxone is available to the public and can be administered through intramuscular (IM), intravenous (IV), and intranasal spray (IN) routes. Our literature review investigates the adequacy of two doses of standard IM or IN naloxone in reversing fentanyl overdoses compared to newer high-dose naloxone formulations. Moreover, our initiative incorporates the experiences of people who use drugs, enabling a more practical and contextually-grounded analysis. The evidence indicates that the vast majority of fentanyl overdoses can be successfully reversed using two standard IM or IN dosages. Exceptions include cases of carfentanil overdose, which necessitates ≥ 3 doses for reversal. Multiple studies documented the risk of precipitated withdrawal using ≥ 2 doses of naloxone, notably including the possibility of recurring overdose symptoms after resuscitation, contingent upon the half-life of the specific opioid involved. We recommend distributing multiple doses of standard IM or IN naloxone to bystanders and educating individuals on the adequacy of two doses in reversing fentanyl overdoses. Individuals should continue administration until the recipient is revived, ensuring appropriate intervals between each dose along with rescue breaths, and calling emergency medical services if the individual is unresponsive after two doses. We do not recommend high-dose naloxone formulations as a substitute for four doses of IM or IN naloxone due to the higher cost, risk of precipitated withdrawal, and limited evidence compared to standard doses. Future research must take into consideration lived and living experience, scientific evidence, conflicts of interest, and the bodily autonomy of people who use drugs.

Keywords Naloxone, Opioid overdose, Literature review

What can we do to prepare?

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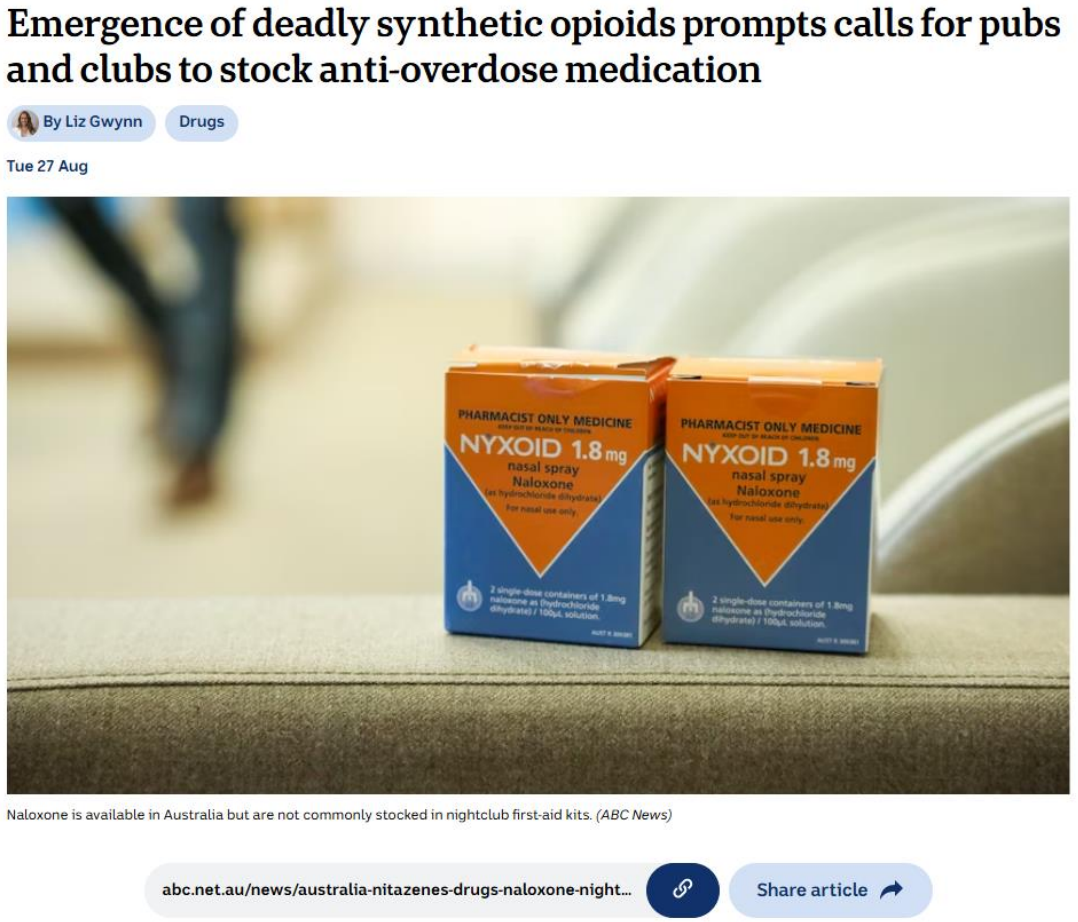
1) Scaling-up Harm Reduction

- **Expanding naloxone** distribution is crucial, great progress but ongoing supply concerns
- **Drug-checking services** (concerns with nitazene test strips, can easily give false negative)
- **Education** campaigns for people who use drugs, particularly non-opioids



Emergence of deadly synthetic opioids prompts calls for pubs and clubs to stock anti-overdose medication

By Liz Gwynn | Drugs

Tue 27 Aug

Naloxone is available in Australia but are not commonly stocked in nightclub first-aid kits. *(ABC News)*

abc.net.au/news/australia-nitazenes-drugs-naloxone-night... Share article

2) Upscale clinical responses: opioid agonist treatment

The **strongest evidence** for reducing mortality is for treatment of opioid dependence is with **opioid agonist treatment** (OAT, oral methadone, sublingual or depot buprenorphine)

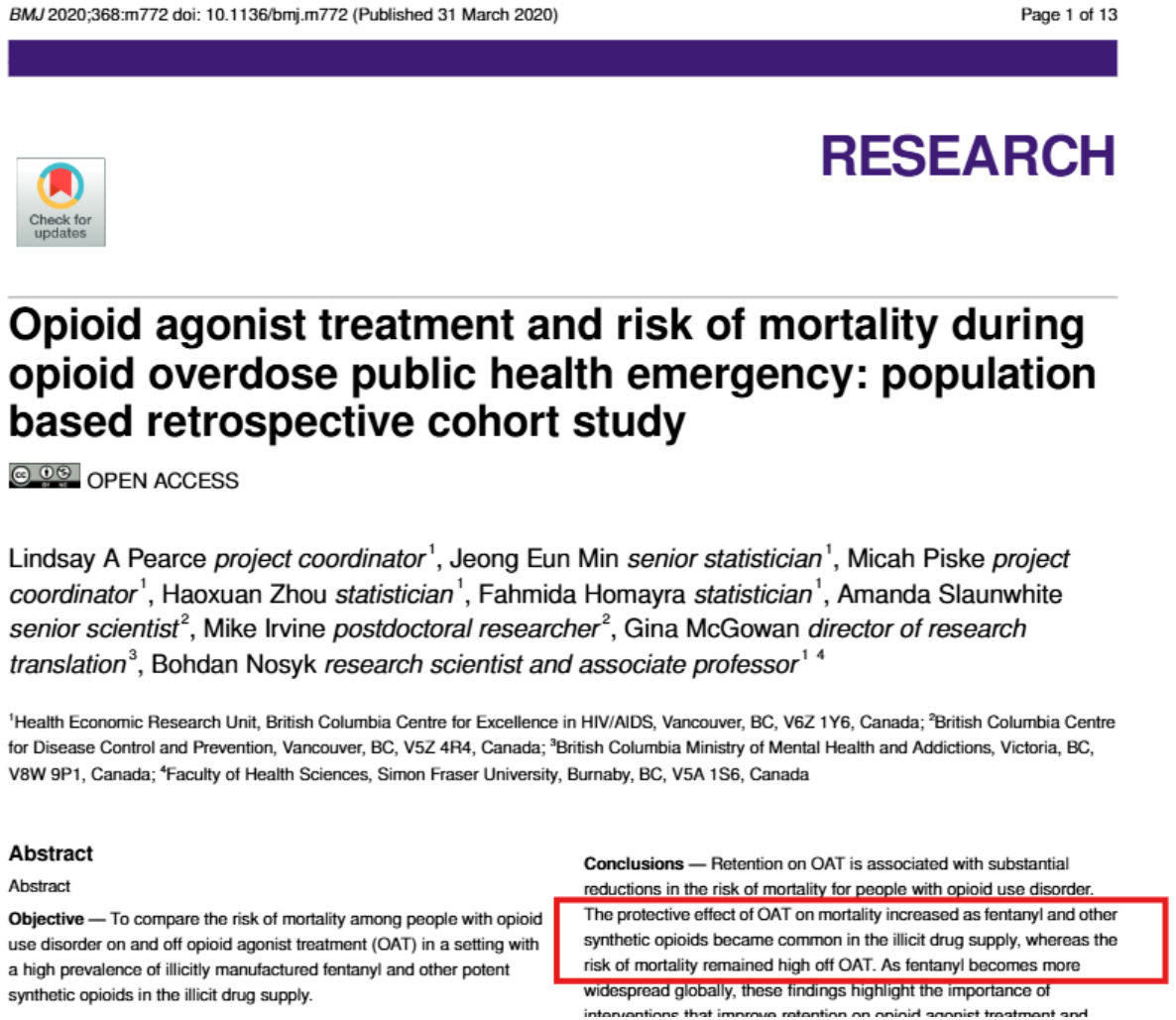
- OAT more protective when NSO in the drug market
- No studies have specifically examined OAT efficacy with nitazenes → evidence from fentanyl's supports OAT works

Need to know:

→ Do challenges with bup induction with fentanyl exist with nitazenes (fentanyl pharmacology differs)?

→ Withdrawal management if nitazenes become common

→ Are new approaches like injectable OAT effective/more effective with a toxic drug market



BMJ 2020;368:m772 doi: 10.1136/bmj.m772 (Published 31 March 2020)

RESEARCH

Check for updates

Opioid agonist treatment and risk of mortality during opioid overdose public health emergency: population based retrospective cohort study

OPEN ACCESS

Lindsay A Pearce *project coordinator*[1], Jeong Eun Min *senior statistician*[1], Micah Piske *project coordinator*[1], Haoxuan Zhou *statistician*[1], Fahmida Homayra *statistician*[1], Amanda Slaunwhite *senior scientist*[2], Mike Irvine *postdoctoral researcher*[2], Gina McGowan *director of research translation*[3], Bohdan Nosyk *research scientist and associate professor*[1 4]

[1]Health Economic Research Unit, British Columbia Centre for Excellence in HIV/AIDS, Vancouver, BC, V6Z 1Y6, Canada; [2]British Columbia Centre for Disease Control and Prevention, Vancouver, BC, V5Z 4R4, Canada; [3]British Columbia Ministry of Mental Health and Addictions, Victoria, BC, V8W 9P1, Canada; [4]Faculty of Health Sciences, Simon Fraser University, Burnaby, BC, V5A 1S6, Canada

Abstract

Abstract

Objective — To compare the risk of mortality among people with opioid use disorder on and off opioid agonist treatment (OAT) in a setting with a high prevalence of illicitly manufactured fentanyl and other potent synthetic opioids in the illicit drug supply.

Conclusions — Retention on OAT is associated with substantial reductions in the risk of mortality for people with opioid use disorder. The protective effect of OAT on mortality increased as fentanyl and other synthetic opioids became common in the illicit drug supply, whereas the risk of mortality remained high off OAT. As fentanyl becomes more widespread globally, these findings highlight the importance of

Future responses: what else do we need to know?

- How and why nitazenes are appearing in our drug market
- Optimal overdose reversal strategies (balance efficacy with avoiding withdrawal)
- Overdose outbreak planning and management

Monitoring community signals of potent synthetic opioids

There has been increased concern about the emergence of potent synthetic opioids like fentanyl and nitazenes in Australia. This project aims to establish a community surveillance system to capture signals of potential presence of these strong opioids to enable a community response.

Please complete the online form if you have information about a signal to report.

This includes information about where the event occurred, what symptoms were observed and what the outcome was. It will take about 5-15 minutes to complete.

Participation in the research project is voluntary.

Only participants who provide online consent will be able to enter data.

Your participation in the study will be confidential.

All the information you provide will be stored securely, accessible only to the research staff. You can provide contact details for clarification of any information you provide if you choose.

What should I report?

The online form will ask questions about the community signal you are reporting, that might suggest novel synthetic opioids are present in the community. For example:

- Unusual overdose
- Unexpected drug effect
- Concerning drug checking result

What service providers and peers see is critical:

Community signals are fast and highly complementary to existing systems that get signals from ED samples and elsewhere

Can be reported anonymously if preferred

Key Takeaways and Urgent Actions

- Nitazenes are a growing threat (drug checking in Victoria could not come soon enough)
- **Naloxone remains effective:** address misinformation, increase access (may have limited time to administer) and education must be expanded to new populations
- Monitoring and rapid response systems likely to be critical

Thank you!

Suzanne.Nielsen@monash.edu