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EDITORIAL

Cychlorphine (*N*-Propionitrile Chlorphine): An Emerging Benzimidazolone Synthetic Opioid and Its Implications for Overdose Recognition and Management

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The United States opioid crisis has evolved through successive waves, each driven by the displacement of one chemical class of illicit drug by the next. Fentanyl and its analogs dominated the third wave; nitazenes[1] – potent 2-benzylbenzimidazole opioids first synthesized in the 1950s, but never approved for medical use – gained significant traction from 2019 onward.[2,3] Following generic scheduling of nitazene analogs by the Chinese government in July 2025, forensic surveillance programs recorded an accompanying decline in nitazene-positive testing and a sharp rise in a structurally distinct class: the "orphine" analogs (benzimidazolone opioids) in particular *N*-propionitrile chlorphine – widely referred to in public health communications as "cychlorphine".[4] The lethality and speed of cychlorphine's emergence make it an urgent novel synthetic opioid (NSO) threat currently facing clinicians, first responders, and public health practitioners.

Cychlorphine ($C_{23}H_{25}ClN_4O$) belongs to the orphine analog subclass – a family of piperidine benzimidazolone opioids structurally related to bezitramide, a 1960s-era pharmaceutical, and to brorphine, the first benzimidazolone NSO identified in illicit drug markets in 2019 and internationally controlled in 2022.[4,5] The core orphine scaffold consists of a benzimidazolone ring system connected to a 4-chlorophenylethylpiperidine group. Cychlorphine is distinguished from its direct parent compound chlorphine by the addition of an *N*(3)-propionitrile (cyanoethyl) group on the benzimidazole nitrogen. This modification alters the compound's receptor interaction profile relative to the parent scaffold.[5] Cychlorphine is thus not a fentanyl analog, a nitazene, or a morphinan derivative; it is its own structural class with a distinct synthetic lineage and pharmacological identity.

The pharmacological characterization of this class rests primarily on studies that characterized chlorphine, brorphine, and related halogenated benzimidazolone analogs. An in vitro and in vivo characterization of brorphine and four structural analogs (orphine, fluorphine, chlorphine, and iodorphine) reported that the compounds bind to the μ-opioid receptor (MOR) with nanomolar affinity, with chlorphine demonstrating the highest binding affinity among the series (K_i = 1.92 nM).[6] In cell-based MOR activation assays (β-arrestin and $G\alpha_i$ recruitment) in HEK 293T cells, chlorphine, brorphine, and iodorphine were the most active agonists, with no significant in vitro biased agonism detected relative to hydromorphone. In vivo, chlorphine and brorphine produce the highest levels of antinociception in mouse hot-plate and tail-flick assays. Critically, respiratory depression assayed by non-invasive plethysmography was most pronounced for fluorphine, chlorphine, and brorphine; and, concerningly, for some compounds, pre-treatment with naloxone (6 mg/kg i.p.) only partially reversed respiratory depression, indicating possible non-opioid contributions to toxicity or receptor kinetics that differ from classical opioids.[6] Similarly partial naloxone reversal of cardiorespiratory impairment induced by these analogs in vivo was reported.[6] The preclinical findings, extrapolated to the *N*-propionitrile modification in

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cychlorphine, suggest a drug with extremely potent MOR agonism, pronounced respiratory depressant capacity, and potentially complex naloxone reversal dynamics in overdose scenarios.

Cychlorphine was first detected by the Center for Forensic Science Research and Education (CFSRE) in August 2024, with confirmatory identification in September 2024 using reference material.[4] The DEA reported its first US detection by a DEA laboratory in Florida in April 2024. By the end of February 2026, DEA laboratories have identified the substance in 22 samples nationally. There was recently a first-report in France.[7] The CFSRE's January 2026 public alert reported *N*-propionitrile chlorphine in 25 blood specimens from fatal overdoses – 21 in the United States and 4 in Canada – with the large majority submitted in the final quarter of 2025 and the first months of 2026. The compound was the sole opioid identified in 11 of those 25 cases. NMS Labs has tentatively identified it in more than 100 toxicology cases.[4] As of March 2026, at least 24 states have reported overdoses or deaths linked to cychlorphine, including a cluster of 19 confirmed deaths in East Tennessee, and detections in Illinois, Ohio, Kentucky, California, and Texas, among others. Co-detected substances in confirmed cases have included fentanyl, oxycodone, methamphetamine, cocaine, novel benzodiazepines such as phenazolam, spirochlorphine, nitazene analogs, and carfentanil – a polydrug context that substantially complicates both overdose presentation and management.[4]

Cychlorphine's emergence follows a now-familiar structural analog substitution pattern. Papsun et al documented this process in detail for the post-fentanyl proliferation of NSOs following core-structure scheduling actions, demonstrating that legislative scheduling of one opioid scaffold reliably predicts the emergence of the next unscheduled class in postmortem casework.[3] Cychlorphine is another iteration of this dynamic: the international control of brorphine in 2022 and the Chinese generic scheduling of nitazenes in mid-2025 created sequential market openings that orphine analogs, led by cychlorphine, have now filled.[4] The UNODC Early Warning Advisory incorporated orphine analogs as a formal new structural group in its February 2026 update, citing detections across 14 countries and 11 confirmed analogs as of early 2026.[8] Cychlorphine is currently not federally scheduled in the United States; its status under the Federal Analog Act as it applies to benzimidazolone structures has not been definitively resolved.

One pressing immediate challenge for clinicians and emergency responders is detection. Standard hospital immunoassay drug screens – designed around legacy opioid scaffolds including morphine, oxycodone, and fentanyl – do not detect benzimidazolone NSOs, and neither nitazene nor fentanyl test strips cross-react with orphine analogs.[8,9] Confirmatory identification requires liquid chromatography coupled to mass spectrometry (LC-MS/MS) with validated reference standards.[9] This analytical hurdle means that deaths attributable to cychlorphine are systematically undercounted. Clinicians should be aware that a negative standard immunoassay in a patient with unexplained opioid-consistent respiratory depression and CNS suppression does not exclude cychlorphine or related benzimidazolone NSOs.

Regarding naloxone efficacy, there is currently no published clinical evidence to support the claim that naloxone is ineffective for reversing cychlorphine overdose. The claim that "naloxone was not able to completely block the antinociceptive effects of chlorphine" derives from a pre-treatment (blocking) study design, not a rescue administration paradigm – a fundamental methodological distinction that has been misrepresented in some public health advisories. Based on in vitro pharmacology showing MOR full agonism with no significant biased signaling,[6] in the absence of counter-evidence, cychlorphine is expected to respond to naloxone as any other MOR agonist does. Multiple doses may be required given its estimated ~10-fold greater potency than fentanyl – the same logic that drives repeat dosing in high-potency fentanyl analog overdoses. The high rate of co-detection with benzodiazepines and stimulants in confirmed cychlorphine fatalities is the more plausible explanation for apparently refractory overdoses, as naloxone does not reverse benzodiazepine-mediated CNS and respiratory depression. Current guidance would seem applicable: administer naloxone promptly, repeat as needed every 2–3 minutes until response or emergency services arrive, and maintain airway support and rescue breathing throughout. To our knowledge no published paper or case report to date has explicitly recorded pupil size in a cychlorphine overdose victim. The only peer-reviewed human case report[2] – describing a 36-year-old man found deeply unconscious with apnea – documents bradycardia, hypothermia, and partial naloxone response, but does not mention pupil findings. Miosis from opioids is mediated by μ-opioid receptor activation in the Edinger-Westphal nucleus of the oculomotor complex, which drives the pupillary sphincter via the ciliary ganglion – a well-established, class-wide effect of MOR agonism. But in severe hypoxia of overdose, CNS hypoxia can override opioid-induced miosis and cause paradoxical sympathetically mediated pupillary dilation.

In summary, cychlorphine represents the leading edge of a new wave of benzimidazolone NSO emergence in the United States drug supply. Its high potency, structural novelty, and detection limitations in standard toxicology screens call for urgent awareness by the clinical, forensic, and public health communities. Expanded LC-MS/MS surveillance capacity, rapid reference standard development, clinician education, and evolving experience regarding naloxone efficacy are pressing needs. The history of the NSO epidemic demonstrates that the window between first detection and widespread problem is short.

Disclosure

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