Clinical Update:

EMERGING DRUGS OF INTEREST: EXPANDED TESTING FOR NOVEL OPIOIDS, DESIGNER BENZODIAZEPINES, SYNTHETIC CANNABINOIDS, AND KAVA USING LONGITUDINAL TOXICOLOGY DATA TO BETTER UNDERSTAND AND SUPPORT INDIVIDUAL RECOVERY JOURNEYS

The illicit drug landscape continues to evolve at a rapid pace. Novel synthetic opioids, designer benzodiazepines, synthetic cannabinoids, and other emerging psychoactive substances can enter the drug supply with little warning, increasing the risk of unexpected intoxication, overdose, and adverse clinical outcomes. Because many of these substances are not detected by traditional drug testing methods, partnering with a laboratory that actively monitors and responds to evolving drug threats is increasingly important. Aegis Sciences Corporation offers testing for the substances highlighted in this article, helping clinicians identify high-risk substance use and make more informed treatment decisions.

Orphines: A Subclass of Designer Opioids

Orphines are a subclass of synthetic opioids originally synthesized in the 1960s during efforts to develop potent analgesic medications. Development of these compounds was ultimately abandoned because of concerns related to respiratory depression and abuse potential. In recent years, however, multiple orphine analogs have emerged in the illicit drug supply as novel psychoactive substances. These compounds act primarily as potent μ-opioid receptor agonists and may pose significant overdose risk due to their potency and limited detectability by conventional testing methods.[1]

Reports from forensic and public health agencies have documented the presence of orphines in counterfeit tablets, powders, and other illicit drug products.[1] As a result, exposure may occur either intentionally or unintentionally, particularly among individuals using substances obtained from unregulated sources (such as counterfeit pills or other illicit drug products).

To support identification of these emerging opioids, Aegis is expanding its Designer Opioid testing panel to include:

- 5,6-Dichloro-Brorphine
- 5,6-Dichloro-Desmethylchlorphine

Copyright © Aegis Sciences Corporation All Rights Reserved

The panel will continue to include these orphines as well:

- Brorphine
- Chlorphine
- N-propionitrile Chlorphine (Cychlorphine)
- Spirochlorphine

Both 5,6-Dichloro-Brorphine and 5,6-Dichloro-Desmethylchlorphine are recently identified benzimidazolone-derived synthetic opioids that have been detected in illicit drug materials. Available laboratory data suggest these compounds exhibit opioid activity at the μ-opioid receptor and share structural similarities with other emerging orphines.[3,4] Although clinical experience remains limited, their continued appearance in the illicit drug supply highlights the need for ongoing surveillance and advanced toxicology testing.[3,4]

From a regulatory perspective, the U.S. Drug Enforcement Administration temporarily placed 5,6-Dichloro-Brorphine, 5,6-Dichloro-Desmethylchlorphine, N-propionitrile Chlorphine, and Spirochlorphine into Schedule I of the Controlled Substances Act in 2026 because of concerns regarding abuse potential and risks to public health.[2]

Continued Evolution in the Nitazene Subclass of Designer Opioids

Nitazenes, also known as benzimidazole opioids, represent another rapidly evolving subclass of synthetic opioids that continues to emerge in the illicit drug supply. First synthesized in the 1950s as potential analgesics, nitazenes were never approved for medical use in the United States. Nevertheless, numerous nitazene analogs have appeared in recent years and have been associated with overdose deaths and severe opioid toxicity.[5]

As clandestine manufacturers continue to modify nitazene structures, new analogs are increasingly being identified by forensic and public health laboratories. One such compound is N-pyrrolidino Ethylene Isotonitazene, a recently identified nitazene analog that has been detected in seized drug materials and toxicology investigations. Available evidence suggests the compound acts as a potent μ-opioid receptor agonist and may present substantial risks for respiratory depression and overdose similar to other nitazenes.[6]

To help identify these emerging substances, Aegis is adding N-pyrrolidino Ethylene Isotonitazene to its Designer Opioid testing panel. The panel will continue to include testing for these nitazenes as well:

- Etonitazene
- Isotonitazene
- Metonitazene
- N-pyrrolidino Etonitazene
- N-pyrrolidino Metonitazene
- N-pyrrolidino Protonitazene

Copyright © Aegis Sciences Corporation All Rights Reserved

- Protonitazene

Given the continued evolution of the nitazene drug class, expanded laboratory testing may provide valuable information when evaluating unexplained opioid toxicity, overdose events, or suspected polysubstance use.[5,6]

Ethylflualprazolam: An Emerging Designer Benzodiazepine

Designer benzodiazepines continue to emerge within the illicit drug market and can present significant clinical concerns because their potency, duration of action, and toxicologic profiles are often poorly characterized. Unlike FDA-approved benzodiazepines, these substances have no approved medical use in the United States and are frequently manufactured and distributed through illicit channels.[7]

Ethylflualprazolam is a novel triazolobenzodiazepine structurally related to both alprazolam and flualprazolam. Limited data are available regarding its effects in humans; however, available evidence suggests it may produce pharmacologic effects similar to other potent benzodiazepines through interaction with GABA-A receptors.[7]

Of particular concern, designer benzodiazepines have been identified in counterfeit tablets made to resemble legitimate prescription medications. Individuals may unknowingly consume these substances when using pills obtained outside of regulated pharmaceutical channels. The presence of designer benzodiazepines can contribute to excessive sedation, cognitive impairment, and an increased risk of respiratory depression when combined with opioids or other central nervous system depressants.[7] As novel benzodiazepines continue to enter the drug supply, laboratory testing capable of identifying these substances may provide valuable information when evaluating unexpected clinical presentations or monitoring patients at risk for polysubstance use.

Emerging Synthetic Cannabinoid AMB-4en-PINACA

Synthetic cannabinoids remain a significant public health concern because they are often substantially more potent than naturally occurring cannabinoids and may produce unpredictable clinical effects. Unlike cannabinoids found in cannabis, synthetic cannabinoids are laboratory-created compounds designed to activate cannabinoid receptors, frequently resulting in more severe toxicity.[8]

AMB-4en-PINACA is an emerging synthetic cannabinoid that has been identified in seized drug materials and biological specimens worldwide. Classified as an indazole-3-carboxamide synthetic cannabinoid, AMB-4en-PINACA acts as a potent cannabinoid receptor agonist and has been associated with severe adverse effects, including agitation, confusion, tachycardia, seizures, loss of consciousness, and other serious toxicities.[8]

Users may be unaware of exposure because synthetic cannabinoids are commonly incorporated into plant material, vaping products, or other products marketed under misleading names. The rapidly changing synthetic cannabinoid market underscores the importance of laboratory testing to identify exposure and aid in the evaluation of unexpected clinical presentations.[8] To help address this emerging trend, Aegis is adding AMB-4en-PINACA to the Synthetic Cannabinoid testing panel.

Copyright © Aegis Sciences Corporation All Rights Reserved

Kava

Kava (Piper methysticum) is a plant native to the South Pacific whose roots contain psychoactive compounds known as kavalactones. Traditionally consumed in ceremonial and social settings, kava has become increasingly available in the United States in the form of beverages, extracts, capsules, powders, gummies, and other commercial products.[9]

Kavalactones are believed to exert their effects through modulation of neurotransmitter systems, including GABA pathways, and may produce relaxation, mild euphoria, sedation, and anxiolytic effects. Reported adverse effects include dizziness, gastrointestinal symptoms, impaired coordination, and concerns regarding hepatotoxicity with prolonged or excessive use.[9]

An emerging trend of particular interest is the combined use of kava and kratom. Commercial products containing both substances are increasingly available through retail and online marketplaces.[10] Recent poison center surveillance has documented a substantial increase in reports involving kratom-containing kava products, with some exposures resulting in serious medical outcomes.[10] Although additional research is needed, the combination may expose users to additive central nervous system effects and other unpredictable toxicities, highlighting the importance of clinician awareness when evaluating patients with suspected botanical or polysubstance use.[9,10]

Supporting Clinical Care Through Expanded Testing

Testing for the substances discussed above is available through Aegis in both urine and oral fluid specimens, providing clinicians with additional tools to identify emerging substance use patterns and support individualized patient care. As the drug supply continues to change, comprehensive toxicology testing can help uncover substances that may otherwise go undetected and contribute to unexpected clinical outcomes. To learn more about testing for these substances and many other emerging drugs, contact your Aegis Regional Sales Manager.

NOTICE: The information above is intended as a resource for health care providers. Providers should use their independent medical judgment based on the clinical needs of the patient when making determinations of who to test, what medications to test, testing frequency, and the type of testing to conduct.

Copyright © Aegis Sciences Corporation All Rights Reserved

References:

1. Kariyawasam-Chavez R. *Emerging Synthetic Opioids: What to Know About Orphines in the Illicit Drug Supply*. Pharmacy Times. Published May 6, 2026. Accessed November 2026.
2. Drug Enforcement Administration. *Schedules of Controlled Substances: Temporary Placement of 5,6-Dichloro Brorphine, 5,6-Dichloro Desmethylchlorphine, N-Propionitrile Chlorphine, and Spirochlorphine in Schedule I of the Controlled Substances Act*. Federal Register. 2026.
3. Walton SE, Khorozov N, Denn MT, et al. *5,6-Dichloro-Brorphine: NPS Discovery New Drug Monograph*. Center for Forensic Science Research and Education; 2025.
4. Walton SE, Denn MT, Quinter AD, et al. *5,6-Dichloro-Desmethylchlorphine: NPS Discovery New Drug Monograph*. Center for Forensic Science Research and Education; 2024.
5. Drug Enforcement Administration, Diversion Control Division. *Benzimidazole Opioids (Nitazenes)*. Drug & Chemical Evaluation Section.
6. Center for Forensic Science Research and Education. *N-Pyrrolidino Ethylene Isotonitazene: NPS Discovery New Drug Monograph*.
7. Walton SE, Khorozov N, Stang BN, et al. *Ethylflualprazolam: NPS Discovery New Drug Monograph*. Center for Forensic Science Research and Education; 2026.
8. Center for Forensic Science Research and Education. *AMB-4en-PINACA: NPS Discovery New Drug Monograph*.
9. Drug Enforcement Administration, Diversion Control Division. *Kava*. Drug & Chemical Evaluation Section. 2026.
10. Towers EB, Williams IL, Holstege CP, Farah R. Increase in Poison Center Reports Linked to Kratom-Containing Kava Products—National Poison Data System, United States, 2000-2025. *MMWR Morb Mortal Wkly Rep*. 2026;75:157-163. doi:10.15585/mmwr.mm7512a1.

Copyright © Aegis Sciences Corporation All Rights Reserved