Clinical Update:

PREVALENT ADULTERANTS FOUND IN THE ILLICIT DRUG SUPPLY

Adulterants are unreported substances added to a product, often to reduce production costs, enhance the products effects, and may increase the severity or likelihood of adverse effects associated with illicit drug use.[1,2] These substances span a wide range of pharmacological categories. While they are most commonly found in combination with illicit drugs, some adulterants have also been detected on their own.[2,3] In 2024, the most prevalent and emergent adulterants at Aegis included xylazine, medetomidine, phenylbutazone, and BTMPS (bis(2,2,6,6-tetramethyl-4-piperidyl)sebacate, also known as Tinuvin® 770).[4] These and other substances are categorized under the "NPS-Other" class within Aegis's Novel Psychoactive Substances (NPS) testing menu. NPS testing enables the ability to conduct real-time monitoring of emerging adulterants, supporting timely public health responses to evolving drug threats.

Xylazine

Xylazine is an alpha-2 adrenergic receptor agonist approved for use as a sedative, with analgesic and muscle relaxant properties, exclusively in veterinary medicine.[5] Its active metabolite is 4-hydroxyxylazine. Xylazine is not a controlled substance and, as such, is not tracked by state prescription monitoring programs. Several branded products contain xylazine, including Anased®, Rompun®, and XylaMed™. On the street, it is commonly referred to as "Tranq" or "Tranq Dope" in the United States and as "Anestesia de Caballo" in Puerto Rico.[5-7]

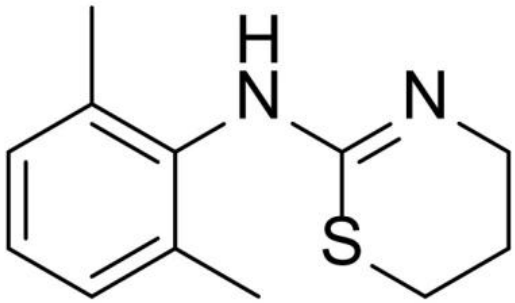

Figure 1: Xylazine Chemical Structure

The Drug Enforcement Agency's (DEA) analysis of over 40,000 illicit drug samples, found the top 5 illicit drugs adulterated with xylazine to be fentanyl (10,746), heroin (2,581), p-fluorofentanyl (2,528), cocaine (723), and methamphetamine (488).[8] Additionally, xylazine co-positivity in fentanyl powder and fentanyl tablets showed a 3-fold and 5-fold increase from Q1 2020 to Q4 2024, respectively.

The use of xylazine as an adulterant in the illicit drug supply is believed to have first emerged in Puerto Rico in the early 2000s, and later appeared in Philadelphia, Pennsylvania (PA) in 2016 within the continental United States (U.S.).[7] In 2021, xylazine was reported in over 90% of the fentanyl samples tested in PA. As of 2024, the DEA found reports of xylazine in all states within the U.S. except for Wyoming (WY).[7,8]

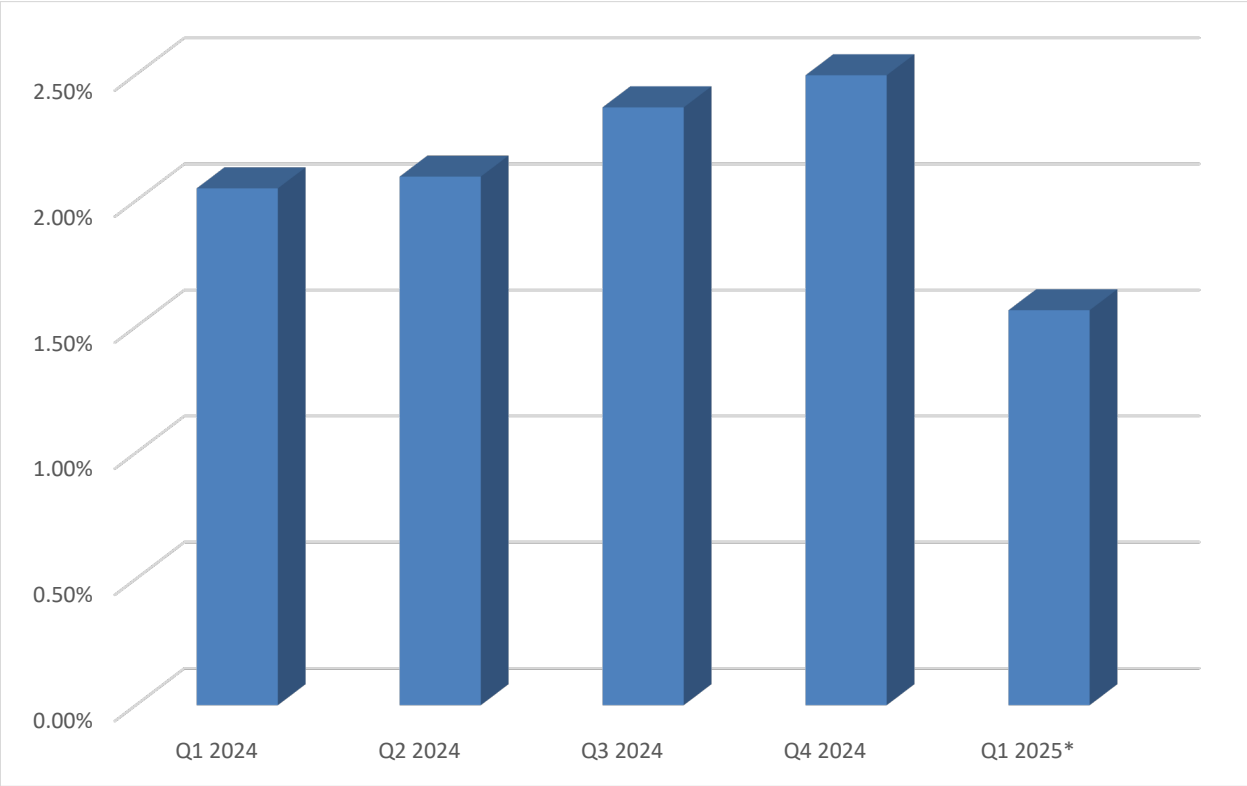

Figure 2: Xylazine Positivity Rates Tested at Aegis

**Q1 through 3/10/25*

Figure 2 illustrates the positivity rate of xylazine, figures 2, 4, 5, and 8 are calculated as (the number of positive results divided by the number of class orders per month, multiplied by 100), over the specified timeframe. Since 2023, xylazine has consistently been the most prevalent adulterant and the most frequently detected NPS at Aegis, regardless of drug class. Although data for Q1 2025 has not yet been compiled, xylazine positivity rates have shown an increase in each quarter of 2024, underscoring the importance of comprehensive, definitive testing strategies to stay ahead of emerging NPS detection trends.

Xylazine is associated with numerous serious adverse effects, including sedation, central nervous system (CNS) depression, respiratory difficulty, severe hypotension, bradycardia, miosis, hyperglycemia, blood clots, rhabdomyolysis, compartment syndrome, and delayed wound healing which is prone to infection.[5,7,9-11] It can also result in severe withdrawal symptoms and death. Repeated xylazine use is linked to chronic skin wounds, such as ulcers that are susceptible to infection and, in severe cases, may necessitate limb amputation.

The danger of xylazine is significantly heightened when combined with opioids like fentanyl or heroin, as it can amplify their sedative effects and greatly increase the risk of fatal respiratory depression.[5,7,9-11] When mixed with other substances such as cocaine, heroin, or additional opioids, it may intensify or prolong their effects, leading to synergistic toxicity.

Although naloxone (Narcan®) does not reverse the effects of xylazine, it is still recommended to be administered in suspected overdose cases, given the frequent co-occurrent adulteration of opioids.[5,7,9-11] Treatment for xylazine intoxication should focus on supportive care, particularly respiratory and cardiovascular stabilization. In severe cases, intoxication may result in life-threatening complications or death. A CDC study from the State Unintentional

Drug Overdose Reporting System (SUDORS) reported a rise in overdose deaths involving illicit fentanyl adulterated with xylazine, increasing from 3% in 2019 to 11% in 2022. Chronic xylazine use can lead to dependence, with individuals using it to avoid withdrawal symptoms such as anxiety, panic, and elevated heart rate or blood pressure. Those initiating opioid treatment with medications like buprenorphine or methadone may require additional support to manage xylazine withdrawal symptoms.

Medetomidine

Medetomidine is a synthetically manufactured alpha-2 adrenergic receptor agonist used exclusively in veterinary medicine as a sedative, muscle relaxant, premedication/anesthesia adjunct, and analgesic.[12-15, 17] It exists in two enantiomeric forms: dexmedetomidine, the active isomer approved for both veterinary and human use, and levomedetomidine, its inactive isomer. Medetomidine's active metabolite, 3-hydroxy medetomidine, also contributes to its pharmacological effects. Medetomidine is not classified as a controlled substance and therefore is not listed in state prescription monitoring programs. Several branded products contain medetomidine, including Domitor®, Zenalpha®, and Placadine™, and it is colloquially referred to on the street as "Rhino Tranq." Medetomidine belongs to the same drug class as xylazine but is 200–300 times more potent and approximately 10 times more selective for the alpha-2 adrenoreceptor.

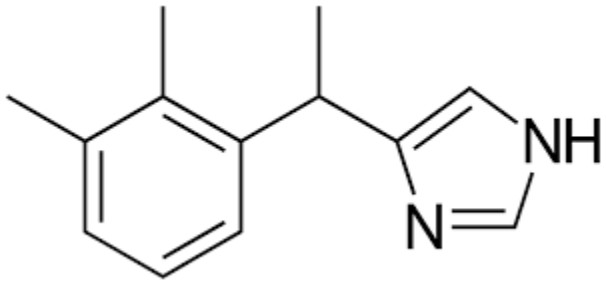

Figure 3: Medetomidine Chemical Structure

Medetomidine was first reported as an adulterant in the illicit drug supply in 2021.[15] It is most commonly found in samples containing fentanyl, heroin, and xylazine, though it has also been identified in combination with more than 15 other substances.[12-16] According to the DEA, from 2021 to 2024, medetomidine and its analog dexmedetomidine have been co-reported with various illicit drugs, including designer opioids, cocaine, synthetic cannabinoids, and methamphetamine.

Reports of medetomidine as an adulterant in the illicit drug supply have come from 13 U.S. states (e.g., California, Colorado, Florida) as well as parts of Canada (e.g., Ontario and British Columbia).[12-16] Its increasing prevalence is evident in DEA data which reported 12 illicit drug submissions testing positive for medetomidine in 2021, rising sharply to 262 in 2022.[15] As of 2023, 208 submissions have been recorded, with final numbers expected to grow. In December 2023, the Center for Forensic Science Research and Education (CFSRE) and the Colombo Plan issued a *Toxic Adulterant Alert* in response to the drug's emergence in the illicit drug supply.[14]

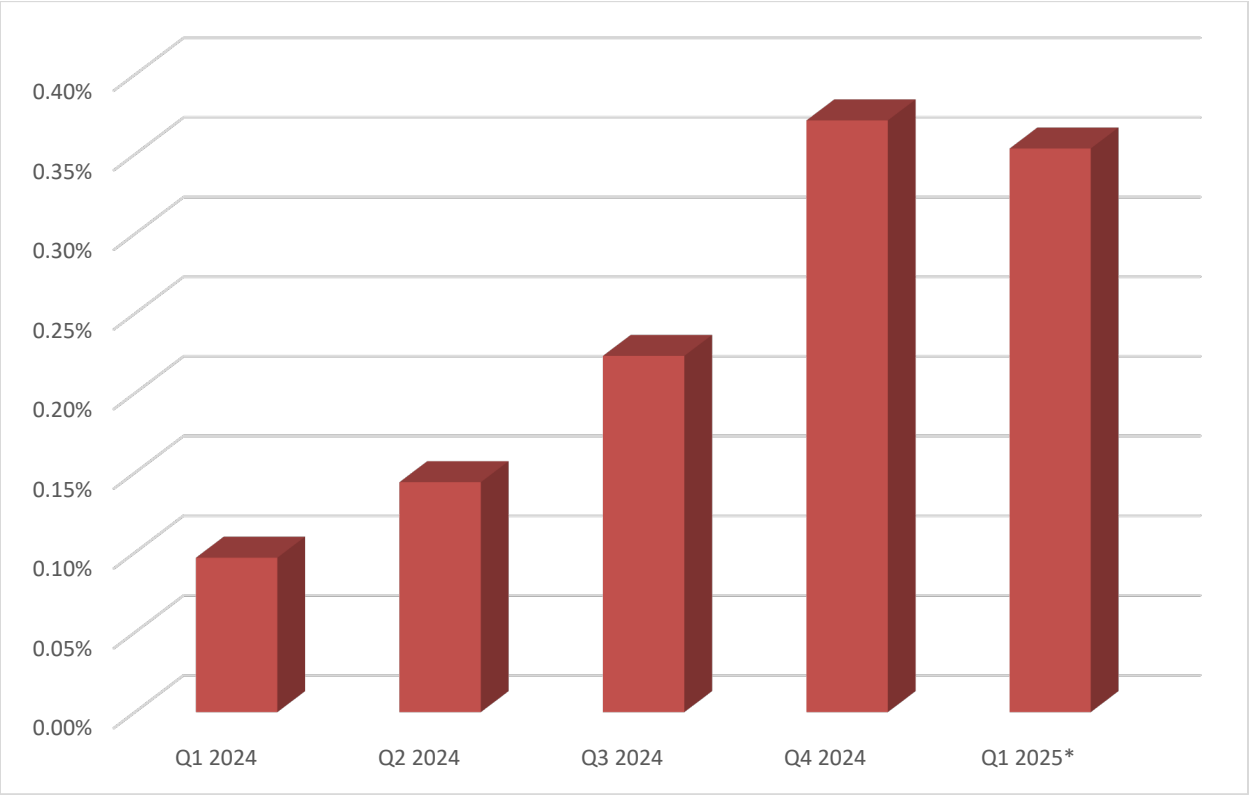

Figure 4: Medetomidine Positivity Rate

**Q1 through 3/10/25*

Figure 4 illustrates a dramatic surge in medetomidine prevalence in 2024, with 97% of positive samples also containing xylazine.[4] As its presence increases, it is essential for healthcare providers to be aware of the associated risks. Providers should consider including medetomidine in routine drug screening panels and review patients' hospitalization history for medically administered dexmedetomidine, as it may cause a positive medetomidine result.[15,16]

Due to the similarities to xylazine, medetomidine is used similarly in veterinary medicine, while dexmedetomidine is used in both human and veterinary settings. Data from the DEA suggests that medetomidine has the potential to supplement or replace xylazine as an adulterant in illicit opioids.[15] However, the combined 219 medetomidine and dexmedetomidine laboratory submissions are minimal compared to the 17,332 xylazine submissions reported in the 2023 interim NFLIS-Drug data (as of June 7, 2024).

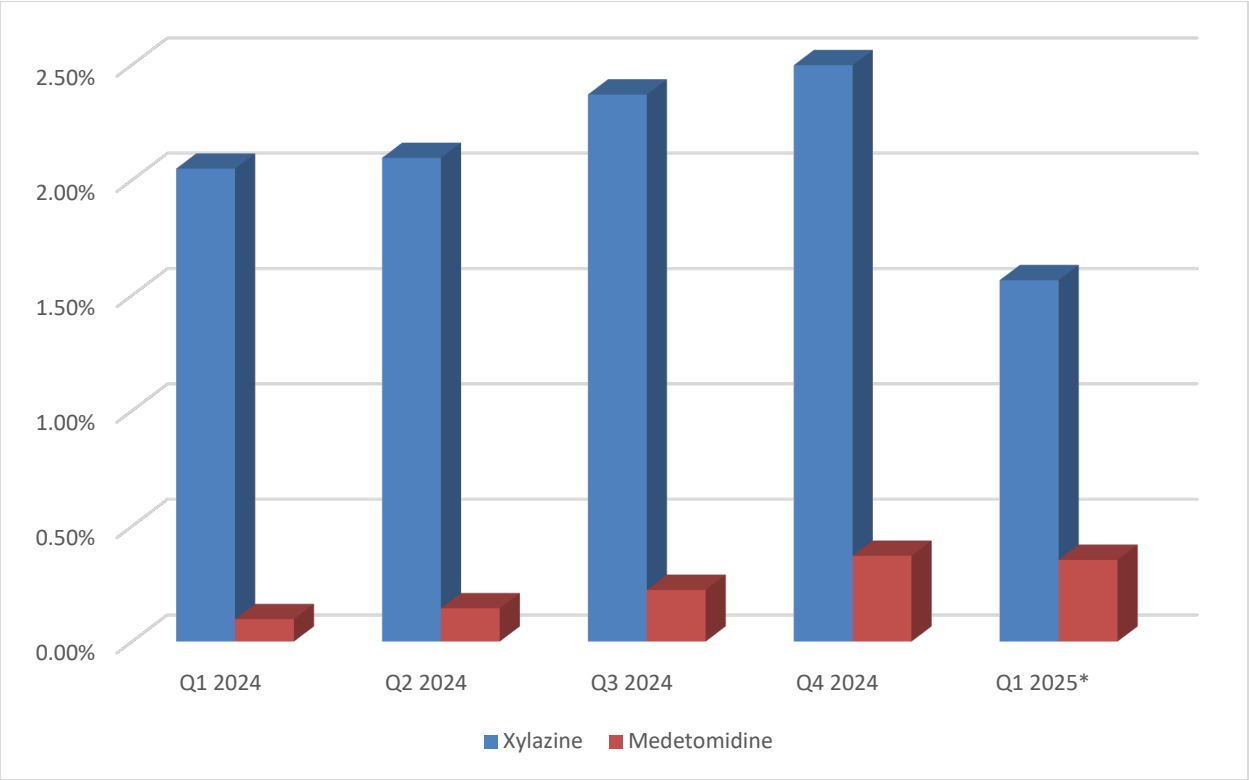

Figure 5: Xylazine vs. Medetomidine Positivity Rate

**Q1 through 3/10/25*

Figure 5 illustrates a quarterly increase in both xylazine and medetomidine positivity rates in 2024 and Q1 2025.

Reported adverse effects of medetomidine include analgesia, sedation, anxiolysis, hallucinations, muscle relaxation, hypotension, and bradycardia.[12-14] In cases where medetomidine has been identified as an adulterant in illicit drugs, severe bradycardia, heightened sedation, and prolonged drug effects have been reported. Adverse events related to medetomidine are reported to last longer than those associated with xylazine, though medetomidine has not been definitively linked to the chronic skin ulcers commonly seen with xylazine use.[15]

During an opioid overdose, the effects of medetomidine are not reversed by naloxone (Narcan®).[15,16] Although reversal agents such as atipamezole and yohimbine exist, their safety and efficacy in humans have not been adequately studied.[14] The treatment of a medetomidine overdose should focus on supportive respiratory care and blood pressure management. It is critical that healthcare providers are aware of medetomidine's emergence as an adulterant in the drug supply and its growing prevalence.[12-16] Given current trends, medetomidine may continue to rise in prevalence and possibly as a substitute or replacement for xylazine.

Phenylbutazone

Our most recent additions to NPS adulterant testing, added in December 2024, include phenylbutazone and BTMPS. Phenylbutazone is a nonsteroidal anti-inflammatory drug (NSAID) formerly used to treat arthritis, gout, and ankylosing spondylitis in humans.[18] However, it has been discontinued for human use in the U.S. and is now approved only for veterinary purposes. Oxyphenbutazone is its active metabolite. Several branded products contain

phenylbutazone, such as Pributazone®, Butequine™, and Butatron®, and it is colloquially known on the street as "Bute." Recent reports suggest its prevalence is increasing across Pennsylvania, prompting concern highlighted in the CFSRE 2003 *Toxic Adulterants alert*.

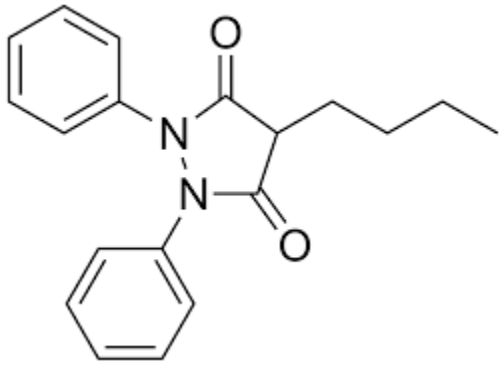

Figure 6: Phenylbutazone Chemical Structure

Phenylbutazone is most frequently found in the illicit drugs heroin, fentanyl, and designer opioids, but has also been found in samples containing cocaine, xylazine and other adulterants.[18] A literature review identified 116 seized drug samples in Pennsylvania from 2016 to 2021 that tested positive for phenylbutazone, highlighting its emerging presence in the illicit drug supply.

Adverse effects contributing to the discontinuation of phenylbutazone for human use include, gastrointestinal bleeding, liver and kidney damage, blood disorders, and reports of death.[18] Long-term use has been associated with hepatitis, kidney failure, and congestive heart failure. Serious blood disorders linked to phenylbutazone include agranulocytosis, leukopenia, thrombocytopenia, and aplastic anemia. Symptoms of toxicity may include rash, blurred vision, nausea/vomiting/diarrhea (NVD), edema, abdominal pain, low blood pressure, confusion, loss of coordination, convulsions, coma, liver failure, and kidney failure. If phenylbutazone is ingested by a non-intravenous route, treatment options such as gastric lavage and activated charcoal may be effective.

BTMPS

BTMPS, also known as bis(2,2,6,6-tetramethyl-4-piperidyl)sebacate, Tinuvin® 770, HALS 770, or T770, is one of the newest emerging adulterants identified in the illicit drug supply as of June 2024.[19-21] It was subsequently added to Aegis testing in December 2024. Animal studies have shown that the mechanism of action of BTMPS is a potent L-type calcium channel blocker and a non-competitive nicotine receptor antagonist. Unlike previously discussed adulterants, BTMPS is not approved by the FDA for any use. It is commonly used as a light stabilizer in a wide range of consumer materials, including plastics, paints, sealants, and packaging. Given its widespread use in these materials, a positive drug test result for BTMPS, particularly in cases where other illicit or unexpected substances have not been identified, should prompt consideration of all potential sources of exposure.

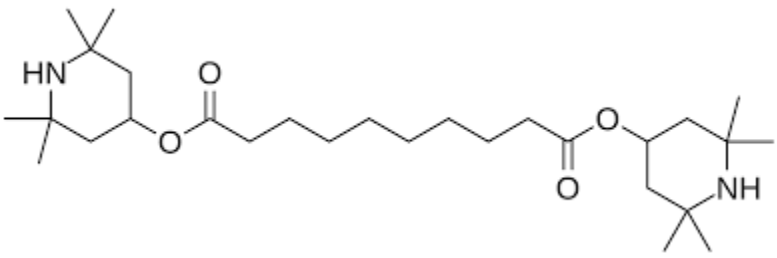

Figure 7: BTMPS Chemical Structure

BTMPS has been detected in the illicit drug supply in substances such as fentanyl, synthetic opioids, stimulants, medetomidine, and xylazine.[19, 21] Analysis of 98 illicit drug samples revealed that in 63% of cases, BTMPS made up more than half of the total volume of the substance. Unlike other adulterants, BTMPS has not emerged from a single location and spread outward; instead, it has appeared simultaneously in multiple states across both the East and West Coasts of the U.S.[21]

Animal studies suggest that BTMPS may cause several adverse effects, including cardiotoxicity, ocular damage, sudden death, and nicotinic antagonist effects.[22] According to a safety data sheet, BTMPS is also suspected of damaging fertility or the unborn child, is highly toxic to aquatic life with long-term effects, and may cause skin irritation.[23] First aid measures vary depending on the route of exposure. In cases of unconsciousness due to inhalation, the patient should be placed in a stable side position for transportation. If the substance comes into contact with skin, it should be washed off immediately with water and soap. In the event of eye exposure, rinse the affected eye thoroughly with running water for several minutes and consult a doctor. If the substance is swallowed and symptoms persist, seek medical attention.

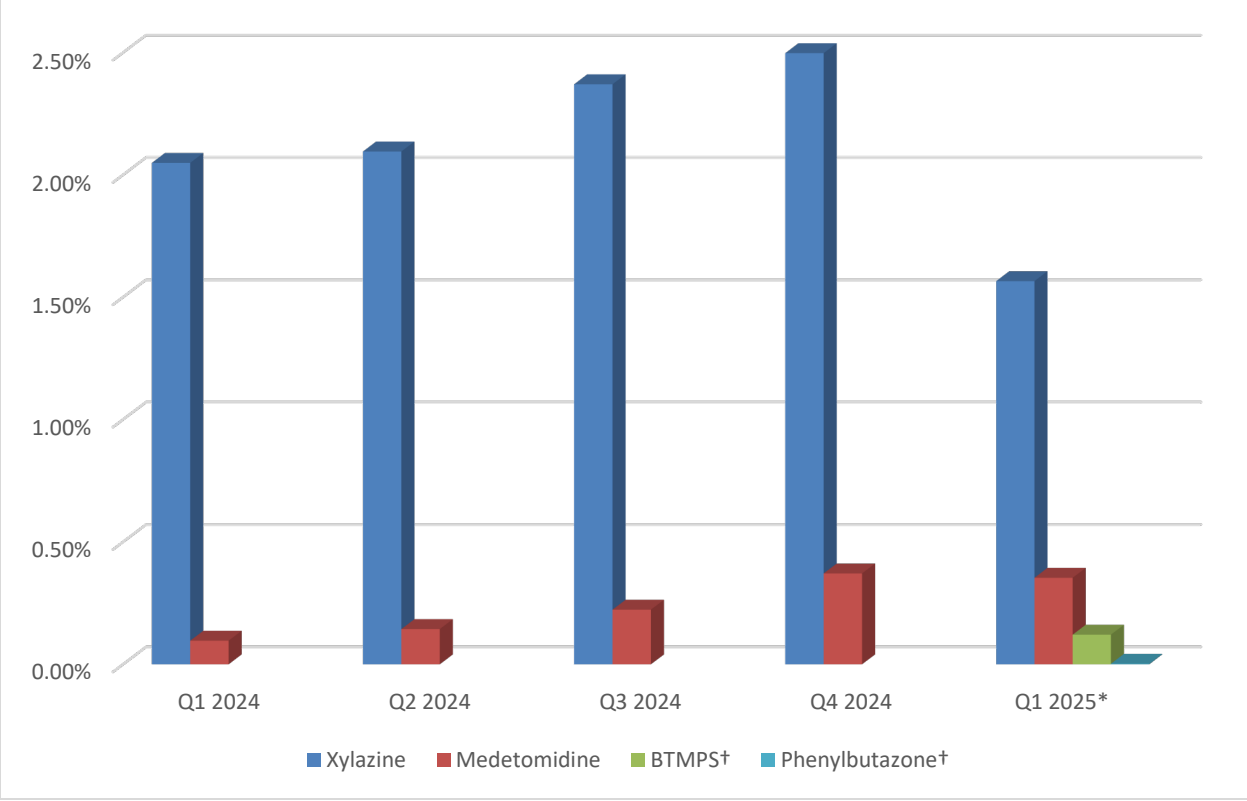

Figure 8: Adulterant Positivity Rates

**Q1 through 3/10/25*

†Date range 12/10/24 through 3/10/25

Figure 8 illustrates the positivity rates of adulterants discussed in 2024 and Q1 2025.

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.

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