Review

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Profound Opioid and Medetomidine Withdrawal: A Case Series and Narrative Review of Available Literature

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Abstract

Medetomidine, a potent veterinary α-2 agonist, has emerged as a fentanyl adulterant in the non-medical opioid supply. Its use has been linked to a novel withdrawal syndrome that is often resistant to conventional treatment protocols. Four cases are presented demonstrating extreme forms of this withdrawal syndrome. A literature review is provided showing both the paucity of available literature as well as potential avenues for treatment and future research. As adulterants continue to proliferate in the illicit drug supply, clinicians should anticipate atypical withdrawal phenotypes and consider early aggressive intervention.

Keywords: medetomidine; xylazine; fentanyl; alpha-2 agonist withdrawal; dexmedetomidine withdrawal; opioid withdrawal; adulterant; sedative withdrawal

1. Introduction

Philadelphia has been at the forefront of the evolving opioid crisis, with illicit fentanyl often contaminated by potent sedatives that complicate withdrawal management [1]. Beginning around 2019, the veterinary tranquilizer xylazine became a ubiquitous fentanyl adulterant – detected in up to 98–99% of tested "dope" samples by 2023 [2]. The combination of high-potency synthetic opioids and xylazine led to unusually challenging withdrawal syndromes and even precipitated withdrawal in patients started on buprenorphine [3]. In response, hospitals in Philadelphia developed novel withdrawal protocols tailored to "tranq dope" (fentanyl/xylazine) users, employing short-acting opioids (e.g., oxycodone or IV hydromorphone), ketamine, antipsychotics for nausea/anxiety (droperidol or olanzapine), and α-2-agonists (tizanidine, or guanfacine) to replace xylazine's effect [4]. Early data showed these protocols were effective during the xylazine era, achieving significant symptom relief and reducing against-medical-advice dispositions (also known as patient directed discharge).

Since mid-2024, however, clinicians in Philadelphia noted a sharp shift in adulterants [5,6]. Medetomidine – a highly α-2- adrenergic agonist used in veterinary anesthesia – largely supplanted

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xylazine as the dominant fentanyl adulterant. This change coincided with Pennsylvania's scheduling of xylazine as a controlled substance, possibly prompting suppliers to substitute medetomidine. Notably, medetomidine is a racemic mixture of dexmedetomidine, a drug used in ICU sedation, and its enantiomer. It is up to 200 times more potent than xylazine as an α-2 receptor agonist [7,8]. By late 2024, laboratory surveillance confirmed medetomidine's widespread presence: 72% of tested opioid samples contained medetomidine (while xylazine prevalence fell to ~30% [6]. Frontline clinicians began encountering fentanyl users with an atypical, severe withdrawal syndrome distinct from opioid- or xylazine-withdrawal [5]. Reported features include intractable vomiting, diaphoresis, tremors, and sympathetic crisis– extreme tachycardia and hypertensive emergencies often refractory to even aggressive treatment for fentanyl and xylazine (other α-2 agonist withdrawal).

Unlike ordinary opioid withdrawal, some patients exhibited altered mental status with periods of stupor (waxing/waning hypoactive encephalopathy) that were surmised to represent posterior reversible encephalopathy syndrome due to severe blood pressure elevation and other cases of demand myocardial ischemia and stress cardiomyopathy. These severe withdrawal presentations were hypothesized to represent medetomidine withdrawal syndrome, analogous to a dexmedetomidine rebound phenomenon, given medetomidine's pharmacology [9]. Alarmingly, previously efficacious treatment protocols seemed ill equipped to manage symptoms, with marked attenuation in reduction of clinical opiate withdrawal scale (COWS) scores [10]. Health officials and clinicians reported that many such patients rapidly deteriorated and required ICU-level care for aggressive symptom management. This emerging medetomidine-linked withdrawal has been deemed life-threatening, often necessitating unprecedented escalations in therapy (e.g., IV infusions of sedatives like dexmedetomidine or anti-hypertensive agents) compared to typical opioid or even xylazine withdrawal.

We describe the care of four individuals with opioid use disorder who developed extreme withdrawal syndromes due to suspected medetomidine-adulterated fentanyl. These cases exemplify the sometimes intractable clinical course of medetomidine withdrawal and highlight the challenges in management of this newly recognized syndrome. We then describe available literature on the human experience with adulterated medetomidine and future concepts in the treatment of severe withdrawal.

2. Materials and Methods

Four cases which were referred by the addiction service to the emergency department quality assurance and peer review committee due to the atypical and unprecedented nature of their clinical course. As all cases were reviewed retrospectively, the cases were reviewed by separate reviewers (KL, GF, EP, DL) and presented from the timeline of arrival in the emergency department through their ultimate departure from the hospital. The senior/corresponding author reviewed each for accuracy and formatting.

We separately conducted a narrative literature review to synthesize current evidence on the management of opioid and medetomidine withdrawal, with an emphasis on the role of alpha-2-adrenergic agonists. The search was conducted by reviewers (KL, DG, PD, SP, JR) using PubMed and Google Scholar on between June 1 and July 1, 2025. Example search terms included: "medetomidine human," "medetomidine fentanyl," "medetomidine adulterant," "medetomidine withdrawal," "dexmedetomidine withdrawal," "opioid withdrawal alpha-2 agonist," "transdermal clonidine," "high dose dexmedetomidine," "low dose dexmedetomidine," "combination dexmedetomidine clonidine," and "combination clonidine tizanidine."

Inclusion criteria were human studies, case reports, case series, observational studies, narrative reviews, and clinical guidelines addressing the human experience with medetomidine exposure, dexmedetomidine use, and use of alpha-2 agonists in withdrawal management. Due to the paucity of research directly examining medetomidine withdrawal, we also included literature on dexmedetomidine, opioid, and alcohol withdrawal as proxy models where relevant. Animal studies were included only where no human data was discovered.

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In addition to indexed databases, we conducted a plain-language Google search to identify relevant grey literature, including continuing education resources and public health advisories. This yielded additional context on emerging clinical practices—such as the use of low-dose dexmedetomidine in non-ICU settings—and public alerts from regional health departments, including the Philadelphia Department of Public Health.

This manuscript was developed in accordance with the CARE guidelines for case reports and the SANRA criteria for narrative reviews to ensure clarity, transparency, and scientific rigor [11,12]. No quantitative synthesis or formal risk-of-bias assessment was performed due to the narrative nature of the review and heterogeneity of the included sources. This study was evaluated by the Thomas Jefferson University Institutional Review Board and was approved given the retrospective and de-identified nature (IRB #1269) of the patient data.

3. Results

3.1. Case One

A 32-year-old female with a past medical history of opioid use disorder (reported use of 8-10 bags/day, taken via insufflation), and denied other relevant past medical history, including a history of other drug use such as cocaine, amphetamines, benzodiazepines, or alcohol, presented to the emergency department (ED) in police custody with symptoms of vomiting, body aches, tremor, and anxiety. She reported she had last used drugs at approximately 14.5 hours prior to arrival, at her usual dose and method. She noted that she was arrested on an outstanding warrant and brought to the police station, whereas she was brought to the hospital several hours later due to onset of severe vomiting and patient report of withdrawal.

Her triage vital signs noted an oral temperature of 98.2 degrees Fahrenheit, HR 134, RR 29, initial blood pressure 143/106 with a pulse oximetry of 99% on room air. Her initial COWS score was documented at 42, denoting severe withdrawal. As per protocol at the hospital, she was ordered standardized severe opioid/adulterant medications: hydromorphone 2 mg IVP, ketamine 10 mg IVP, diphenhydramine 25mg IVF, olanzapine 10 mg ODT, lactated ringer's IV solution 1000 mL, acetaminophen 1000 mg PO, gabapentin 300 mg PO, tizanidine 4 mg PO. Due to profuse vomiting, she was unable to take the oral medications but received all IV medications and fluid. Given inability to tolerate the olanzapine, she was also given droperidol 5 mg IVP x 1 to help try to get vomiting under control. Her vital signs were then noted to dramatically worsen, developing a HR first of 166 and as high as 205, with RR of 45, with relatively mild hypertensive blood pressure, 118/98. ECG demonstrated sinus tachycardia, a rate of 164, PR interval 128 ms, QRS interval 70 ms, QTc interval 488 ms with non-specific, favored rate-related, repolarization changes.

Due to this severe worsening, she was given serial doses of medication to better control her withdrawal. These included, over a 90 minute period: diazepam 10 mg IVP, hydromorphone 10 mg IVP, diazepam 10 mg IVP, acetaminophen 1000 mg IVPB and hydromorphone 20 mg IVP. The sum total impact on her vital signs was that her RR went from 29-46 prior to these medications, to a documented RR of 16. She was still noted to be wide awake, tremulous, anxious, and complaining of severe pain. At that point, her other vital signs were: BP: 134/60, HR: 170, SPO2 = 97% on RA and a temperature of 100.8 degrees Fahrenheit.

Her withdrawal only seemed to worsen, requiring additional medications over the next two hours: hydromorphone 10 mg, diazepam 10 mg IVP, hydromorphone 10 mg IVP again, diazepam 10 mg IVP again, hydromorphone 6 mg IVP, diazepam 10 mg IVP, all before being placed on dexmedetomidine, then fentanyl and finally midazolam infusions. Dexmedetomidine infusion began with escalating titration leading to ceiling dose (1.5 mcg/kg/hr) within 90 minutes after onset. Due to lack of response (patient was wide awake), she was also started on a fentanyl and finally midazolam infusions at within two hours after reaching maximal dexmedetomidine dose. Her COWS at that point had improved, but was still markedly elevated at 27. She was also administered 2x 0.3mg/24

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hour clonidine transdermal patches, an additional 2000 mL of IVF (1000 mL of 0.9% normal saline, 1000 mL of Lactated Ringer's solution) and admitted to the medical intensive care unit.

Of note, her diagnostic evaluation revealed normal electrolytes with a serum bicarbonate of 18 and an anion gap of 23, normal hepatic function tests, positive urine fentanyl, benzodiazepine and opiate screens (obtained following provision of hydromorphone, diazepam but before dexmedetomidine and fentanyl), and a white blood cell count of 32,600 with a 94% neutrophilic predominance as well as a thrombocytosis to 654,000 with a normal hemoglobin/hematocrit (12.3/36.9). AP One View Chest X-Ray was read as no evidence of pneumonia, pneumothorax or mediastinal abnormalities and urine/blood cultures were negative on gram stain and final analysis. Leukocytosis improved to 23,700 the following day and 10,000 by hospital day four, with thrombocytosis improving, but not resolved (459,000) by hospital day eight.

During her ED care she received, over six hours, a total of 58 mg of IVP hydromorphone, 50 mg of IVP diazepam, 10 mg of ketamine IVP and rapidly titrated infusions of dexmedetomidine, fentanyl (switched to hydromorphone after one hour) and midazolam. Patient's vital signs remained markedly abnormal (tachycardia, tachypnea) and she never required intubation in the ICU despite being on maximally dosed infusions of dexmedetomidine, fentanyl and midazolam until they were weaned down over the subsequent 72 hours while oral medications (buprenorphine, clonidine, gabapentin, hydroxyzine) were titrated up.

After infusions were discontinued, she continued to work with the addiction team and social workers to find a safe disposition for her to a sober living house, with instructions to continue buprenorphine, tizanidine as well as a clonidine taper. She suffered no adverse events and never required respiratory support despite being on maximal doses of three parenteral infusions. Subsequent liquid chromatography-tandem mass spectrometry revealed positive detection of 3-hydroxy-medetomidine metabolites in her urine.

3.2. Case Two

A 44 year old female who was brought to the ED by ambulance, as an anonymous patient, for altered mental status with concern for substance use/intoxication. Paramedics noted Glasgow Coma Scale (GCS) of 13: she was alert but disoriented on initial evaluation. Her vital signs upon presentation to the ED showed moderate hypertension, but were otherwise stable (T 97.3 degrees F, HR 70, BP 142/102, RR 14, SpO2 98% on RA). She quickly became markedly hypertensive (231/138 mmHg) and tachycardic (166). Her mental status also worsened; she was described as increasingly agitated and combative despite multiple doses of intravenous hydromorphone (total ED dose = 10 mg), droperidol (5 mg), diphenhydramine (50 mg), midazolam (10 mg), and ketamine (360 mg). A COWS score of 33 was recorded approximately four hours after initial presentation. Urine drug screening was positive for fentanyl, cocaine, benzodiazepines, and amphetamines.

A dexmedetomidine infusion was started to treat suspected α-2-agonist withdrawal. Despite the maximal dosing (1.5mcg/kg/hr) of dexmedetomidine as well as additional 6 mg doses of IV hydromorphone (12 mg total over 3 hours), the patient remained agitated with severe vital sign abnormalities. Hence, the decision was made to intubate the patient for airway protection, and to allow for more even more aggressive medical intervention. Intravenous propofol (10-100 mcg/kg/hr) and fentanyl (50-500 mcg/kg/hr) infusions were added at that time, which were also soon brought to maximal parameters. The patient was subsequently admitted to the medical intensive care unit (MICU).

Approximately one hour following intubation, with three active infusions, she remained agitated, pulling at tubes and lines. Per the admission history, "… pt was intubated [and placed] on max dose of fentanyl, Precedex, and propofol. [Alert and] still moving all extremities unpurposefully." A midazolam infusion was added to the patient's regimen at this time, which reached as high as 10 mg/hr.

The addiction service was consulted the following morning for additional recommendations. Through active engagement, staff were able to locate and contact the shelter at which the patient had

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been staying; staff there were able to identify the patient and provide additional recent history. Chart review under the patient's name confirmed opioid use disorder history, with the patient reporting injection use of up to 3-4 bundles (45-60 bags) per day of fentanyl/α-2-agonists at a recent hospital admission. She was also frequent user of stimulants (cocaine and methamphetamine), with a past history of alcohol use as well.

At the time of initial addiction specialty evaluation, her medication regimen had stabilized on the four infusion regimen. Enteral medications were added via orogastric tube, including standing clonidine (0.3 mg q8), tizanidine (6 mg q8), Oxycodone 20mg q4h and diazepam 10mg q8h were added to some effect. A buprenorphine micro induction was also started to assist with weaning the full opioid agonists being used (fentanyl and oxycodone), starting at 150 mcg q6 hours.

Early on hospital day 3, the patient was again noted to have episodes of severe agitation despite the above regimen. A third 0.3 mg clonidine patch was added and infusions were titrated up. She made repeated requests for extubation despite her condition being noted as critical and developing fevers (102.7 degrees F) and a productive cough.

Later in the afternoon of hospital day 3, the patient self-extubated after maximal doses of dexmedetomidine and fentanyl were reached. Despite the regimen of sedating medications she was receiving, she was described by the MICU team as awake and alert, requesting to be discharged from the hospital. After extensive discussion with the patient about risks and benefits of discharge vs continued admission, the patient was found to have capacity and left the hospital that evening, her condition was regarded as poor.

3.3. Case Three

A 40 year old Male was brought by ambulance to the ED from a municipal bus with reports of vomiting, tremor and concern for opioid and α-2-agonist withdrawal. Initially he was not able to provide further history other than to say he did not remember when he last used. Initial vital signs showed a blood pressure of 213/99 mmHG, a respiratory rate of 24, HR of 97, temperature 97.2 degrees F and pulse oximetry of 98% on room air. His initial COWS was documented at 24. After 4 mg of IV hydromorphone, 10 mg of IV ketamine, olanzapine 10 mg ODT, ondansetron 4 mg IV and the application of a 0.3 mg clonidine transdermal patch, patient was noted to have a COWS score of 29. His blood pressure (215/144 mmHg) and heart rate worsened, the latter dramatically, first to 170, then consistently between 180-200, with a maximum of 217. It was a regular, narrow complex tachycardia. Electrical cardioversion was attempted after the patient had no response to additional doses of hydromorphone, midazolam and IV fluid (2L of Ringer's Lactate), but patient remained with severe tachycardia. Patient received 20 mg of hydromorphone, 15 mg midazolam, and subsequently a dexmedetomidine infusion, reaching maximal dose (1.5 mcg/kg/hr) within 3 hours.

Propofol (100 mcg/kg/hr), Midazolam (10mg/hr, increased to 16mg/hr) and fentanyl infusions were ordered (500 mcg/kg/hr), and quickly titrated to maximum. The sum total of these interventions brought patient's heart rate to 120-130s and their blood pressure to 140/104 mmHg. He was subsequently intubated for refractory encephalopathy and airway protection and was admitted to the MICU.

His hospital course was complicated by upper gastrointestinal bleeding (thought related to critical illness) and bilateral pneumonia. After extubation on hospital day number 6, patient underwent micro induction of buprenorphine starting at 150 mcg buccal q6 and ending on 8 mg sublingual BID. He was maintained on both clonidine orally and transdermal, and oral diltiazem was added to assist with what was deemed a persistent atrial tachycardia by cardiology. He was connected with social services for shelter placement and follow up at the Stephen and Sandra Sheller Bridge clinic to help continue his medical and substance recovery.

3.4. Case Four

A 32 year old male with a past medical history of Opioid Use Disorder (16 bags/day via insufflation), prior Alcohol Use Disorder, nicotine dependence and reported schizoaffective disorder

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presented to the ED due to uncontrolled withdrawal symptoms: nausea, vomiting, tremors to upper and lower extremities along with uncontrolled anxiety. He reported that he last used 4 hours prior to arrival in the ED. He denied using other intentional substance including cocaine, cannabis, methamphetamines, benzodiazepine or alcohol. Patient was reportedly brought into the emergency room by a friend who was concerned about his health and his intention to go through self-imposed withdrawal with hopes of achieving sobriety. Two months prior to this admission, the patient was treated in a separate facility for Hypertensive Urgency, Hypokalemia, and complicated Opioid Withdrawal and required Intensive Care Unit (ICU) level of care and was treated with a dexmedetomidine infusion.

His triage vital signs were temperature of 97.5 degrees F, HR 86, RR 18, SPO2 98% on room air, and BP 121/79 mmHg. His urine drug screen was positive for fentanyl and methadone only (though methadone was given prior to sample collection). Initial Clinical Opioid Withdrawal Scale (COWS) was 7 then progressed to COWS of 15 within 90 minutes. The patient was given Ketamine 50 mg IVP, hydromorphone 4 mg IVP and Methadone PO 30 mg to address withdrawal. Despite these medications, the patient's COWS increased to 22 within the hour. The patient continued to exhibit restlessness, agitation, vomiting, piloerection, diaphoresis and vital abnormalities. Repeat vitals indicated a HR of 113 and BP of 165/71. The patient again received 4 mg IVP of hydromorphone along with 1 mg IVP of lorazepam in response. The decision was made to start dexmedetomidine IV infusion at 0.7 mcg/kg/hour to address patient's uncontrolled withdrawal symptoms and continue with hydromorphone 4 mg IVP (total 12 mg in 3 hours). He was admitted to the medical intensive care unit for further intervention and management. Unfortunately, his withdrawal only seemed to worsen as his COWS peaked at 27 with a HR 123 and BP of 173/94 on maximally dosed dexmedetomidine.

On hospital day 2, the Addiction Medicine Service was consulted for withdrawal recommendations given the patient's high opioid and alpha 2 agonist sedative requirements. The patient was unable to tolerate oral medications and hence was treated aggressively with IV medications. During day 2 the patient would receive a total of 62 mg of IV hydromorphone, maximal rate (1.5 mcg/kg/hour) IV dexmedetomidine, 0.9 mg of clonidine transdermal (3 patches), 5 mg of IVP lorazepam and 10 mg of IVPB methadone. Despite these medications, the patient's lowest COWS was 10. The patient's Glasgow Coma Scale (GCS) was noted to be 15 throughout the day and the patient's level of alertness range from being alert and calm to mildly drowsy except for sleeping hours.

On hospital day 3, the addiction Medicine team followed up with the patient and the patient indicated that his withdrawal was now better under control and he was able to tolerate oral medications. The patient requested a medically managed withdrawal process with the hopes of weaning completely off opioids (including methadone and buprenorphine), sedatives and related adjuncts. Adjustments were made to the patient's opioid and dexmedetomidine regimen based on his goals of care. For day 3, the patient received a total of 10 mg of IVPB methadone, 20 mg of PO methadone, 25 mg of IVP hydromorphone, 2 mg of IVP lorazepam, 10 mg of PO olanzapine (given for withdrawal insomnia) along with 0.9 mg of clonidine via transdermal patches and 0.3 mg of oral clonidine.

For hospital day 4 the patient continued with planned tapering of his medications. Unfortunately, on day 5 of admission, the patient stated that he would no longer continue with the medically managed withdrawal process and requested to be discharged from the ICU. He was offered to be referred to an inpatient drug and alcohol rehabilitation facility or to have an intake scheduled with an outpatient methadone clinic. The patient politely declined. As per the medical team's documentation, the patient was alert, oriented and capable of understanding the benefits versus the risks of his request to be discharged from the hospital and his decision not to continue with treatment for Opioid Use Disorder. At the time of the discussion, patient's COWS was reportedly 10. The patient was discharged after he was seen by a social worker who assisted him in getting a bus pass.

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4. Discussion

4.1. Summary

The patients described above exemplify the perilous features of the human experience of medetomidine withdrawal syndrome. Despite receiving timely, high-dose treatment for opioid and α2 agonist withdrawal when identified, the patients suffered persistent or worsening withdrawal symptoms with uncontrolled autonomic dysfunction. Such extreme tachycardia and tachypnea, accompanied by tremors, anxiety, and protracted vomiting, often refractory to even multiple sedative agents, are not seen in uncomplicated opioid withdrawal [5,6,9].

4.2. Introduction to Narrative Review

Managing this syndrome requires a fundamentally different approach and intensity of care than ordinary opioid withdrawal. Our patients' deterioration prompted early transfer to intensive care and initiation of a dexmedetomidine infusion, alongside opioid and other sedative infusions, to achieve symptom control. In a larger cohort of patients with suspected medetomidine withdrawal, over 90% of patients needed ICU care and almost a quarter required mechanical ventilation [5]. Notably, dexmedetomidine proved to be a cornerstone of therapy – as it directly replaces the missing alpha agonists, allowing gradual down-titration and mitigation of withdrawal, until patients are able to tolerate oral intake and can be switched to clonidine, tizanidine or another oral alpha agonist. Of note, there is a paucity of literature to support many of these treatments given the novelty of this exposure and condition in human history. As such, the literature cited are association and correlation, hypothesis generating, and by no means are any of these concepts rigorously studied.

4.3. Pharmacology and Comparison to Xylazine

Medetomidine is a racemic mixture of dexmedetomidine and levomedetomidine, used in veterinary medicine for its safe therapeutic window and potent sedative and analgesic properties. Dexmedetomidine, the more pharmacologically active enantiomer, is FDA-approved for human use and widely administered for procedural and ICU sedation [13,14]. Dexmedetomidine is a highly selective α2-adrenergic receptor agonist that produces sedation and analgesia through distinct but overlapping central mechanisms. Its sedative effects are primarily mediated in the pons (locus coeruleus), where activation of presynaptic α2-adrenergic receptors inhibits adenylate cyclase via G-protein coupling [15]. This leads to decreased release of norepinephrine, disinhibiting GABAergic neurons in the thalamus, creating sedation.

Analgesia is mediated at both spinal and supratentorial levels. In the dorsal horn of the spinal cord, dexmedetomidine inhibits the release of nociceptive neurotransmitters like substance P and glutamate by acting on presynaptic α2 receptors. Concurrently, it activates postsynaptic α2 receptors, thereby decreasing excitability and pain transmission [16]. Supraspinal actions also contribute to pain modulation. Dexmedetomidine's high α2:α1 selectivity ratio (~1600:1) underlies its targeted pharmacologic profile, providing effective sedation and analgesia with reduced risk of α1-mediated side effects or significant respiratory compromise [17].

At higher doses, medetomidine can suppress atrioventricular (AV) nodal conduction, increasing the risk of significant bradycardia and conduction delays, particular those with underlying heart conditions or on other AV nodal blocking therapies [18]. Although human pharmacokinetic data are limited, medetomidine follows a similar profile to dexmedetomidine. Intramuscular administration results in rapid absorption, with peak plasma concentrations occurring within 10 to 30 minutes [19]. Intravenous administration of both drugs have similar onset and duration and half lives between two and three hours[20,21].

As previously stated, medetomidine is also at least 200 times more potent than xylazine, its veterinary predecessor in the street drug supply [22–25]. Both agents produce dose-dependent

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sedation, bradycardia, and hypotension via central α2-receptor activation, but medetomidine is also more lipophilic and exhibits a longer duration of action.

It is primarily metabolized by the liver, has an elimination half-life of approximately 1.6 hours, and produces sedation lasting 2 to 3 hours, which may be potentiated with co-administered opioids [26]. This synergism is thought to contribute to its growing presence as an adulterant in illicit fentanyl, potentially enhancing or extending the experience for users.

Xylazine withdrawal and treatment are more widely described than medetomidine and include use of short acting opioids, replacement alpha agonists with clonidine, tizanidine and guanfacine and other adjunctive medications [4,27–29]. While some have recommended benzodiazepines and other sedatives for the treatment of this condition [30] we have generally recommended against this practice, due in part to the co-occurring risk of tolerance and respiratory depression, given the less morbid nature of xylazine withdrawal, and greater success with more conventional treatments and doses.

4.4. Dexmedetomidine Withdrawal Syndrome

Dexmedetomidine withdrawal syndrome is increasingly recognized in critically ill adults following prolonged or high-dose infusions. Characteristic symptoms include agitation, anxiety, rebound hypertension, and tachycardia, typically emerging within hours of abrupt discontinuation, particularly after infusions exceeding 48 hours [31,32]. This phenomenon was first described in two ICU patients, with symptoms developing 4–6 hours post-infusion and resolving after alpha-2 agonist re-initiation[31]. Others have similarly reported withdrawal-related sympathetic hyperactivity, including that rebound hypertension is common and a potentially severe manifestation[32–34].

Abrupt cessation can also lead to increased pain sensitivity, possibly due to the loss of dexmedetomidine's modulatory effects on central arousal pathways [35]. In a pilot study, scheduled clonidine tapers significantly reduced withdrawal incidence and severity in ICU patients [36]. A larger review confirmed these findings and advocates for proactive planning in cases involving long-term dexmedetomidine use[37].

Although these data reflect medically and surgically ill patients in the ICU setting, these findings remain relevant for managing medetomidine withdrawal, where abrupt cessation may mirror infusion discontinuation without tapering. Understanding the physiologic consequences of withdrawal from potent α2-agonists underscores the need for carefully titrated substitution strategies.

4.5. Timeline and Epidemiology

While medetomidine has circulated in veterinary practice since the 1990s, its appearance in the illicit opioid supply appears to be a recent phenomenon. Laboratory surveillance first detected it in North American drug samples in 2022–2023, with a sharp rise beginning in 2024. In Philadelphia, medetomidine prevalence increased from 29% to 87% of opioid-positive samples between May and November 2024, eventually reaching 72% of all tested opioid samples by late 2024 [6,38]. A separate series of atypically intoxicated individuals from Pennsylvania was also published in early 2025 [39]. This coincided with the Pennsylvania state scheduling of xylazine, suggesting a substitution effect by drug suppliers.

Additional outbreaks have been documented elsewhere in the U.S. A May 2024 cluster in Chicago identified 12 patients with medetomidine-associated overdose, including multiple cases of bradycardia, altered mental status, and minimal naloxone response [40]. In Pittsburgh, a cohort of 23 patients presented with severe, refractory withdrawal symptoms in late 2024, prompting toxicological confirmation of medetomidine exposure via LC-MS/MS testing [41]. Lastly, a larger cohort was recently published that demonstrated symptoms correlated to concentration of urine medetomidine metabolites, but not xylazine metabolites [42].

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4.6. Concepts in Clinical Management

No published treatment protocol exists for medetomidine withdrawal. A few papers have included treatment guidance, which involves co-treatment of opioid withdrawal and alpha-2 agonist withdrawal [5,9,43,44] using aggressive amounts of oral and intravenous alpha-2 agonists. A separate website, maintained by members of the University of Pennsylvania, is dedicated to up to date expert guidance on management of medetomidine withdrawal [45]. Below are a series of novel concepts that either relate to treatments provided in the above cases or are avenues for future research.

While not well described in the literature, the hallmark symptoms: vomiting and sympathetic dysregulation are frightening both in their severity and in the rapidity of their onset [XX]. Individuals who have been monitored for intoxication or for other complaints seem to go from benign appearance to life threatening presentations within hours and sometimes as few as 1-2 hours. Focusing on early perturbations in vital signs (such as new tachycardia or hypertension) before other physical signs develop has been postulated as warning signs. Given the difficulty of controlling symptoms following the onset of vomiting, we and other experts recommend early use of oral and IV treatments before severe symptoms develop, as they often are easier to prevent than control.

While xylazine withdrawal has been shown to be controllable with less potent alpha-2 agonists like tizanidine and guanfacine [4], medetomidine has seemingly mandated the use of the most potent commonly available oral alpha agonist, clonidine. Given the huge volumes individuals are using, supratherapeutic doses of clonidine are also being used, with individuals in severe withdrawal sometimes requiring 0.6 – 0.9 mg doses of clonidine every 1-2 hours until symptoms are controlled. Future studies should assess use of these dosages to assess safety and therapeutic ceiling.

4.7. Combination Alpha-2 Agonist Therapy

Emerging evidence supports the synergistic use of combined α_2-adrenergic agonists to achieve enhanced therapeutic efficacy, potentially minimizing adverse effects and dosages [9,46–48]. Fairbanks et al. demonstrated clear synergy between clonidine and dexmedetomidine, reporting significantly greater antinociceptive effects in combination compared to either drug alone, attributable to separate activation of α_2A- and α_2C-adrenoceptor subtypes [46]. Similarly, combined clonidine and tizanidine [9], despite limited direct clinical evidence, share overlapping analgesic mechanisms by inhibiting spinal substance P release, a critical mediator of nociceptive transmission [49]. Co-administration of these α_2-agonists allows clinicians to optimize treatment efficacy while reducing dose-dependent side effects and allowing safer titration to solely oral medications [47–49]. This synergistic approach is particularly valuable in clinical contexts where maximal drug dosing is reached, or limited due to tolerability concerns, offering practical advantages in managing complex withdrawal syndromes involving potent α_2-agonists like medetomidine.

4.8. Low Dose Dexmedetomidine Infusion Outside the ICU

Dexmedetomidine infusions, typically administered in intensive care units (ICUs), are emerging as a feasible option for use at lower doses (typically up to 0.7 mcg/kg/hr) in non-ICU settings, such as progressive care units or step-down floors. Literature exploring adjunctive use of dexmedetomidine in severe acute alcohol withdrawal supports its safe and effective administration outside the ICU, demonstrating minimal adverse safety events and improved patient management compared to standard therapies alone [50]. Similarly, critical care nursing associations are starting to highlight successful experiences with dexmedetomidine in non-ICU settings, citing controlled sedation and reduced agitation without respiratory depression or significant cardiovascular instability [51]. Another study discussed use of low-dose dexmedetomidine for as an adjunct to a multi-modal regimen for those with significant opioid tolerance [52]. As such, low-dose dexmedetomidine infusion represents an emerging therapeutic modality for safely transitioning stable patients from intensive care or supporting individuals who cannot tolerate oral alpha-2 agonists (e.g., clonidine or tizanidine) but do not require intensive care level management. Additional

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studies should assess the safety and efficacy profile of low-dose dexmedetomidine outside the ICU setting.

4.9 High Dose Dexmedetomidine

Mounting clinical experience supports intravenous dexmedetomidine as a core intervention for managing refractory withdrawal syndromes due to α_2-agonist adulterants like medetomidine. Although standard package dexmedetomidine dosing ranges from 0.2–1.5 mcg/kg/hr [53], clinical reports suggest higher doses—up to 2.5 mcg/kg/hr—may be required to adequately control severe agitation and autonomic instability [53–58]. Supporting this practice, Kobayashi et al. demonstrated that critically ill adults tolerated dexmedetomidine infusions up to 2.5 mcg/kg/hr without increased adverse events [54]. Similarly, Tobias summarized pediatric and adult experiences safely utilizing higher-dose dexmedetomidine in ICU sedation and withdrawal contexts [55], while Shehabi et al. reported successful use of "supratherapeutic" dexmedetomidine dosing in deeply sedated ICU patients without notable respiratory depression or bradycardia [56]. The pharmacokinetic work shared by Iirola et al. also demonstrate evidence of linear human metabolism at doses up to 2.5 mcg/kg/hr [57]. Clinically, these higher doses are frequently administered concurrently with opioids (e.g., fentanyl, hydromorphone), allowing eventual step-down to oral medications as withdrawal symptoms subside. Future research should assess whether a higher ceiling doses of dexmedetomidine could prevent the need for, or lower the doses of, concurrent infusion sedative/analgesic agents.

4.10. Transdermal Clonidine

Transdermal clonidine patches offer continuous α_2-adrenergic agonist delivery, effectively mitigating withdrawal symptoms in settings where oral medications are not tolerated due to severe vomiting or altered mental status. The caveat to this is that delayed duration of action, often requiring 18-24 hours after placement to see evidence of therapeutic effect [59]. This approach has been successfully employed as a bridging strategy for patients transitioning from ICU-level sedation with dexmedetomidine, as well as in outpatient opioid withdrawal management [60–62]. Literature demonstrates that clonidine patches reduce withdrawal severity by providing sustained sympatholytic activity without significant adverse effects, such as severe hypotension or bradycardia [59,60]. In clinical scenarios of other alpha-2 agonist withdrawal, the clonidine patch has been effectively used to prevent rebound sympathetic hyperactivity, facilitating smoother transitions to oral medications or discontinuation altogether [62–64].

4.11. Public Health Implications and Future Directions

The rapid rise of medetomidine as a fentanyl adulterant—and the severity of the withdrawal it induces—represents a significant public health challenge. Traditional opioid withdrawal algorithms, even those adapted for xylazine, are insufficient in this context. Regional protocols in Philadelphia have already been updated to include earlier addiction and ICU consultation, higher opioid dosing, aggressive combination oral and transdermal alpha agonist therapy, and routine use of dexmedetomidine infusions for refractory withdrawal.

Testing for medetomidine is limited to specialized LC-MS/MS platforms [5,39,42,44], which may delay confirmation. Still, clinicians encountering withdrawal syndromes with extreme sympathetic features (e.g., unexplained hypertension, HR >180, persistent vomiting, altered mental status) should consider medetomidine exposure and escalate care accordingly. Physicians and public health advocates strongly recommend increasing funding and innovation in the fields of testing and treatment for this condition [65].

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5. Conclusion

Severe medetomidine withdrawal presents with often refractory sympathetic activity and can require the use of seemingly heroic doses and combinations of medical treatments to control, with variable success. Potential treatment options include replacement of alpha agonists, combination alpha agonists, high and low-dose dexmedetomidine and transdermal therapies. These are often required across a continuum of care spaces, including the ICU, and require careful titration to assure symptom control and safe use. Future studies are required to assess viability of novel treatment options and public health leaders should maintain vigilance surrounding adulteration of illicit drug supplies.

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Abbreviations

The following abbreviations are used in this manuscript:

Abbreviation	Full Term
ICU	Intensive Care Unit
ED	Emergency Department
$\alpha 2$	Alpha-2 (adrenergic receptor)
ECG	Electrocardiogram
HR	Heart Rate
SBP	Systolic Blood Pressure
DBP	Diastolic Blood Pressure
COWS	Clinical Opiate Withdrawal Scale
PHA	Public Health Alert
PCU	Progressive Care Unit
CNS	Central Nervous System
PO	Per Os (by mouth/oral)

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IVP	Intravenous Push
QTc	Corrected QT Interval
SANRA	Scale for the Assessment of Narrative Review Articles
CARE	CAse REport guidelines
GABA	Gamma-Aminobutyric Acid
LC-MS/MS	Liquid Chromatography–Tandem Mass Spectrometry
AV	Atrioventricular
DEA	Drug Enforcement Administration

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