

Medetomidine as a Fentanyl Adulterant: Pharmacology, Detection, Clinical Presentation, and Management

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Systematic Review

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Abstract

Purpose of review: Medetomidine is a veterinary α 2-adrenergic agonist that has been an adulterant of illicitly manufactured opioids since 2022. We review its pharmacology, detection, intoxication, withdrawal, and management, and assess why severe withdrawal has emerged in some regions but not others.

Recent findings: Medetomidine has spread through North American drug markets yet evades most toxicology testing. Roughly 200 times more potent than xylazine, with greater α 2 selectivity and imidazoline-1 activity, it causes intoxication resembling other α 2 agonists: sedation and bradycardia. The dominant clinical problem is withdrawal: autonomic dysregulation, intractable vomiting, and encephalopathy frequently requiring intensive care. Treatment requires multimodal α 2-agonist therapy, often escalating to parenteral dexmedetomidine. Where it is established, withdrawal encounters and hospital admissions have risen.

Summary: We hypothesize that both local prevalence and drug concentration determine where withdrawal appears. This syndrome exposes gaps in both assessment and treatment; prospective multicenter research, a validated withdrawal instrument, and integrated addiction-critical care models are needed.

Introduction

The unregulated drug supply in the United States has become increasingly dynamic, with the shift to illicitly manufactured fentanyl followed by a proliferation of adulterants added to extend sedation or to mimic and potentiate opioid effects [1, 2]. These adulterants have steadily complicated clinical and public health. Initially, the veterinary α 2-adrenergic agonist xylazine introduced distinct wound and sedation complications and raised unresolved questions about withdrawal management [2-6]. Now medetomidine, a more potent α 2 agonist, has displaced xylazine in several U.S. regions [7]. Its emergence has been geographically heterogeneous but profound. Medetomidine was first detected in forensic samples in 2022 and spread across more than a dozen states within two years. In some cities, it overtook xylazine and became prevalent in fentanyl samples within months of arrival. Following a string of atypical overdoses, a severe withdrawal syndrome started to rise [8-14]. This rapid change has challenged treatment systems and forced patterns of care to adapt quickly, as protocols developed for the xylazine era have proven insufficient for medetomidine-associated withdrawal [15, 16].

Peer-reviewed evidence has not kept pace, making it critical to share clinical experience now and build system-level resilience to future shifts. In this narrative review, we synthesize the literature on medetomidine as a fentanyl adulterant, covering its pharmacology, detection in the illicit supply, acute intoxication and overdose, the withdrawal syndrome, and current management. Where the evidence base is thin, we draw on our experience in Philadelphia and Pittsburgh, Pennsylvania, two of the most-affected cities.

Methods

We searched PubMed, Scopus, and Google Scholar from January 2015 through August 2026 for literature on medetomidine as an adulterant in the illicit drug supply, using combinations of the terms "medetomidine," "fentanyl," "adulterant," "withdrawal," "opioid overdose," and "alpha-2 agonist." Given the publication lag, we supplemented peer-reviewed literature with grey literature from local and national sources. We included case reports, case series, and observational studies of medetomidine intoxication, overdose, or withdrawal in humans, and, given the absence of randomized trials, studies of iatrogenic dexmedetomidine withdrawal in critical care. Reference lists were hand-searched. We used the Scale for the Assessment of Narrative Review Articles (SANRA) to guide our approach [17].

Results

We identified 82 sources, with evidence types summarized in Table 1.

Table 1: Evidence types identified in the literature search.

Evidence type	n	Description
Original clinical studies	18	Case reports, series, and retrospective analyses of medetomidine intoxication, overdose, and withdrawal in humans, including the multicenter case series, the ICU-utilization and QTc analyses, and maternal-neonatal cases
CDC field reports	4	Regional reports of emergence and clinical clusters in Missouri/Colorado/Pennsylvania, Chicago, Philadelphia, and Pittsburgh
Forensic and drug-checking studies	5	Peer-reviewed analytical and toxicologic characterization of the illicit supply and biospecimens, including enantiomer differentiation and a naturalistic pharmacokinetic study
Public health alerts and surveillance	14	CDC, CFSRE, PDPH, and Pennsylvania Groundhogs alerts and drug-checking reports, a federal diagnostic coding agenda, plus one news report, tracking the rapid spread of medetomidine
Pharmacology and pharmacokinetic studies	18	Preclinical and human studies of α_2 and imidazoline pharmacology, receptor selectivity, and dexmedetomidine pharmacokinetics
Reviews, commentary, and editorials	9	Narrative reviews and perspectives on medetomidine, xylazine, and the evolving opioid supply
Guidelines, consensus, and clinical tools	5	Consensus management statements, a systematic review, and validated withdrawal assessment scales
Background and comparator literature	6	Xylazine epidemiology, clonidine pharmacology, and a reference text
Pending publication	3	--
Total	82	

Pharmacology

Medetomidine is a racemic 1:1 mixture of dexmedetomidine, the pharmacologically active S-(+)-enantiomer, and levomedetomidine, the inactive R-(-)-enantiomer [18]. Dexmedetomidine alone is approved by the U.S. Food and Drug Administration for short-term sedation in surgical and critical-care settings in humans; the racemate is approved only for veterinary sedation and analgesia, with no human indication [18, 19]. In the illicit supply, medetomidine is consistently recovered solely as the racemic mixture [20, 21].

Receptor pharmacology

Medetomidine can be understood in comparison to xylazine, a veterinary α_2 agonist also detected in the illicit fentanyl supply, and clonidine, an α_2 agonist commonly used off-label in the management of opioid withdrawal. All three are central α_2 -adrenoceptor agonists, reducing sympathetic outflow through presynaptic inhibition of norepinephrine release in the locus coeruleus and producing sedation, analgesia, anxiolysis, and sympatholysis [18, 22]. They differ, however, in two clinically relevant properties (Table 2).

Table 2. Comparative Pharmacology of α_2 -Adrenergic Agonists Relevant to Acute Care

Agent	$\alpha_2:\alpha_1$ Selectivity	Relative α_2 Potency	I1 Receptor Activity	Elimination Half-life	FDA Approval	Clinical Relevance
Medetomidine (racemate)	~1620:1	~200× xylazine	Yes (imidazoline class)	2–3 h (active enantiomer)	Veterinary only	Dominant emerging fentanyl adulterant; severe withdrawal syndrome
Dexmedetomidine	~1620:1	~200× xylazine	Yes	2–3 h (healthy adults); 2–4 h (critically ill)	ICU sedation; sublingual for agitation in schizophrenia/bipolar	Pharmacologically active enantiomer of medetomidine; cornerstone of parenteral withdrawal management
Xylazine	~160:1	Reference	No (thiazine)	~30–50 min	Veterinary only	Prior dominant adulterant; necrotic skin wounds; distinct withdrawal syndrome not clearly established
Clonidine	~220:1	~10× xylazine	Yes	6–24 h	Hypertension; ADHD; off-label opioid withdrawal	Mainstay oral therapy; biphasic overdose pattern (hypertensive then hypotensive)

Selectivity ratios derived from receptor binding studies; potency comparisons are approximate and dose-dependent. Half-lives reflect typical adult values; clinical effects may persist beyond pharmacokinetic estimates in critical illness or polypharmacy. I1, imidazoline-1 receptor

The first difference is $\alpha_2:\alpha_1$ selectivity. Medetomidine has a selectivity ratio of approximately 1620:1, compared with 220:1 for clonidine and 160:1 for xylazine [18, 23]. Medetomidine is thus approximately ten-fold more α_2 -selective than xylazine and, on a dose-for-dose basis, up to two hundred times more potent as an α_2 agonist [18, 23]. Greater α_2 selectivity translates clinically to more profound sedation, pronounced bradycardia and hypotension, and less α_1 -mediated peripheral vasoconstriction. The pathophysiology of xylazine-associated wounds is incompletely understood, though experimental work suggests it may be related to a direct action on epidermal keratinocytes through the kappa opioid receptor rather than to α_1 -mediated vasoconstriction [24]. Whatever the mechanism, the lower incidence of necrotic wounds with medetomidine than xylazine is confounded by frequent co-detection of both agents [15, 25]. Medetomidine binds with similar affinity across the α_2A , α_2B , and α_2C subtypes [26].

The second difference, less discussed but potentially important, is imidazoline-receptor activity. Medetomidine is chemically an imidazoline type α_2 agonist and, like clonidine, binds the imidazoline-1 (I1) receptor in the rostral ventrolateral medulla [18]. Xylazine, a thiazine derivative, does not have meaningful affinity for this site. I1 receptor activity may contribute to the prolonged sympatholytic characteristic of clonidine overdose and is a plausible mechanistic contributor to the autonomic rebound that defines the medetomidine withdrawal syndrome [27]. Notably, while the biphasic hemodynamic pattern described with clonidine overdose (an initial hypertensive phase followed by sustained hypotension) has been observed in medetomidine intoxication, sinus bradycardia and either normo- or hypotension tend to predominate and are hallmark features [28]. The contribution of I1 agonism to these clinical features has not been formally investigated and is a priority for mechanistic study.

Pharmacokinetics

Human pharmacokinetic data for medetomidine are derived primarily from small phase I studies conducted in the late 1980s, where intravenous medetomidine was compared with clonidine in healthy volunteers [29–32]. Peak sedative effects appear within 15–45 minutes of intravenous administration and resolve within approximately four hours; hemodynamic effects resolve by three hours, faster than with clonidine [29, 30, 32]. Extrapolating from a study of dexmedetomidine, the bioavailability of medetomidine likely is high following intravenous, nasal, and buccal administration but is limited by extensive first-pass metabolism after oral ingestion [33]. Illicit use is most often by injection, inhalation, or insufflation. Because dexmedetomidine is the pharmacologically active component of the racemic mix, human pharmacokinetic data can also be applied to the active fraction of illicit exposure. Dexmedetomidine is 94% protein-bound, undergoes rapid initial distribution followed by an elimination half-life of 2–3 hours in healthy adults and 2–4 hours in the critically ill, is metabolized primarily through UGT1A4- and UGT2B10-mediated N-glucuronidation, with CYP2A6 involvement in hydroxylation. It is primarily renally excreted as metabolites, 3-OH-medetomidine and its glucuronidated form [19, 34]. A recent study assessed medetomidine pharmacokinetics in 13 patients presenting to emergency departments in Massachusetts, primarily with fentanyl and xylazine intoxication. Initial medetomidine blood concentrations, available for 5 patients, were 25 ± 24 ng/mL, with calculated half-life ranging from 148 to 353 min [35].

Variability in the illicit supply

Forensic surveillance data indicate that medetomidine content in illicit samples varies across time and between individual samples. In the Mid-Atlantic region tracked by CFSRE, the mean medetomidine content in fentanyl-primary samples increased approximately three-fold across 2025, from approximately 5% to approximately 15% by weight, with substantial sample heterogeneity among individual measurements [4]. Variable concentration is also a plausible mechanism for the unpredictable presentations seen in patients with similar use patterns, and complicates generalization [21].

Detection and Control in the Illicit Drug Supply

Geographic Emergence and Spread

Medetomidine was first identified in Maryland in 2022, with the initial outbreak confined to that state [7]. Sporadic detections followed across Missouri, Colorado, Pennsylvania, and California through 2023 [8]. A CFSRE public alert in May 2024 described rapid proliferation of medetomidine in drug samples from multiple states and linked medetomidine adulteration to overdose outbreaks [36]. Over the course of 2024, medetomidine emerged as the dominant α_2 agonist adulterant in the illicit opioid supplies of Philadelphia and Pittsburgh, with confirmed medetomidine-associated toxicity also reported in Chicago [9-12, 37], alongside parallel detections across multiple additional U.S. states [38]. International spread has also been documented, with detections reported in Toronto and Vancouver in early 2024 and ongoing surveillance in Canadian jurisdictions [18, 39]. In 2025, medetomidine was also identified in the United Kingdom [40].

National surveillance through NFLIS shows a steep trajectory concentrated in the Northeast and Midwest, with the South reporting 17% detection and the West less than 1% [13]. By late 2025, CDC Overdose Data to Action wastewater and drug-product testing had detected medetomidine across at least eighteen states, and the authors identified at minimum, twenty-six states and the District of Columbia with detection in the illicit fentanyl supply or in biospecimens from people who use drugs [3, 9, 13, 38]. In New York, medetomidine was first detected in May 2024 and was identified in 25.1% of opioid samples analyzed through December 2025, peaking at 44.1% in May 2025 [41].

Local Surveillance: Philadelphia as a Sentinel Site

Philadelphia has served as a sentinel site for medetomidine emergence because of coordinated drug-checking infrastructure that predated the adulterant shift. The Philadelphia Department of Public Health (PDPH) Division of Substance Use Prevention and Harm Reduction has operated in partnership with CFSRE since 2020 and with the Pennsylvania Groundhogs Group (PAG), a community-based drug-checking program. PDPH issued successive advisories identifying medetomidine in the local supply (May 2024) [42], describing the emerging withdrawal syndrome (December 2024) [43], providing management guidance (June 2025) [44], and, most recently, guidance for outpatient management (June 2026) [45]. Published PDPH syndromic surveillance data from April 2025 linked the rise in medetomidine detection to increases in substance-use-related emergency department visits [46]. Hospital-based data corroborate this signal. Monthly encounters treated with a standardized opioid withdrawal order set at two Philadelphia emergency departments more than doubled across the era transition, while the predominant presentation shifted from wound and soft tissue complaints to withdrawal itself [47]. PAG quantitative trend reports have complemented this surveillance [48].

Philadelphia drug-checking data have tracked the substitution of medetomidine for xylazine in near real time. From the first quarter of 2024 through the fourth quarter of 2025, the proportion of fentanyl-primary samples containing xylazine fell from 97% to 21%, while the proportion containing medetomidine rose from negligible levels to 88% [4, 49]. Fentanyl itself remained present in essentially all samples, although its mean purity declined over the medetomidine era, falling across Pennsylvania from approximately 14% in 2023 to roughly 7% by 2025 [4, 50].

Beyond formal drug-checking programs, front-line clinical recognition has also driven the original detection of medetomidine in several regions. A reported cluster of patients with bradycardia and hypotension in Worcester, Massachusetts, for example, led clinicians to obtain blood samples that confirmed medetomidine exposure and triggered coordinated public health communication [51]. Such local responses are vital given the deep variability of community penetrance.

Detection Methods and Limitations

Forensic identification of medetomidine in drug samples and biological specimens relies on varied forms of gas and liquid chromatography-mass spectrometry, through targeted approaches [7, 21, 36]. Enantiomeric determination is feasible but only employed by a few laboratories and has forensic implications: illicit samples contain racemic medetomidine, a signature that distinguishes non-medical exposure from iatrogenic dexmedetomidine and is confirmable in postmortem and clinical specimens [20, 21]. Point-of-care medetomidine

test strips have been developed and validated with 100% sensitivity in preliminary evaluations [20], though their utility depends on proper sample preparation and is limited in regions where medetomidine prevalence is already ubiquitous.

Clinical detection faces different constraints. Medetomidine is not included in standard hospital toxicology panels, which typically use immunoassays, delaying timely diagnostic confirmation. Diagnosis of intoxication or withdrawal in the hospital are clinical. With confirmation available only through mass spectrometry testing, turnaround times often preclude augmentation of real-time decision-making [15, 20]. Administrative identification should improve in the near term, as ICD-10-CM codes for toxic effect of medetomidine (T65.85-) are approved for implementation on October 1, 2026, though a distinct code for medetomidine withdrawal remains under consideration [52].

Regulatory Status

Medetomidine is approved by the U.S. Food and Drug Administration only for veterinary use and is not currently a federally scheduled controlled substance. Some have linked the Philadelphia xylazine-to-medetomidine transition to Pennsylvania's 2024 scheduling of xylazine, consistent with a substitution pattern in which scheduling one adulterant creates market incentive for its successor [16, 53]. The association is not clear, and there is evidence to suggest the shift may be pharmacologically driven (Fig. 1). Since xylazine remains present in a substantial minority of Philadelphia samples, the impact of adulterant scheduling should be assessed alongside other hypotheses.

Acute Intoxication and Overdose

Acute medetomidine toxicity in the adulterated fentanyl supply follows predictably from its pharmacology, though the clinical picture is shaped by near-universal co-exposure to fentanyl and variable exposure to xylazine and other adulterants [4, 14, 25]. Diagnosis rests on pattern recognition in patients with suspected opioid exposure [28] (see Fig. 2).

Clinical Presentation

Following medetomidine-fentanyl exposure, patients may present with depressed mental status and hypoventilation consistent with mu-agonist effects. Following reversal of opioid-mediated respiratory depression, however, a second, distinct phase may develop: prolonged deep sedation that persists despite adequate ventilatory drive, accompanied by sinus bradycardia, and hypo- or normotension [14, 28, 54]. In a Philadelphia case series of eleven patients presenting with suspected opioid overdose, sinus bradycardia was the most consistent finding and resolved without atropine, pacing, or vasopressor support [54]. In multicenter data, exposure was independently associated with bradycardia (adjusted OR 4.03, 95% CI 1.35-10.58) among emergency department patients with overdose [55]. Hypotension and even severe bradycardia (30-40 beats/min) are often well tolerated with supportive care or observation alone [27]. Three case reports from Chicago described a similar picture of persistent sedation and bradycardia after naloxone administration in patients with confirmed medetomidine exposure [56]. A reported association between medetomidine and hallucinations, drawn from drug-checking surveys, is inconsistently seen in hospital-based clinical experience [57].

Respiratory depression, when present, is primarily attributable to the opioid component rather than to medetomidine itself, consistent with the minimal direct respiratory effects of α_2 agonists [18, 19].

Management of Intoxication and Overdose

Management of acute medetomidine intoxication is supportive. Naloxone should be administered and re-dosed as needed to restore and maintain adequate ventilation, with dosing titrated to respiratory effort rather than to level of arousal, since medetomidine-mediated sedation will not reverse regardless of naloxone dose [28, 58]. Attempts to achieve full arousal through escalating naloxone carry the risk of precipitating opioid withdrawal without addressing the underlying α_2 -agonist effect. Aspiration precautions, including elevation of the head of the bed and placement in the recovery position, are reasonable given prolonged sedation. A small subset of patients may require endotracheal intubation for airway protection, though most do not [14, 28]. Intravenous isotonic fluid therapy is generally sufficient for blood pressure support; vasopressors are rarely required for signs of hypoperfusion [28]. Telemetry monitoring is reasonable but unlikely to alter management.

Atipamezole, a selective α_2 antagonist approved as a veterinary reversal agent, is not available for human use and has not been systematically evaluated in this setting [18]. Although reversal may appear attractive, an α_2 antagonist risks precipitating a severe withdrawal syndrome, which is more morbid than the intoxication itself. Supportive care remains standard.

Withdrawal Syndrome

Medetomidine withdrawal is the most clinically consequential feature of the current adulterated supply. It differs from opioid, xylazine, and other sedative withdrawal in both tempo and phenomenology, and drives the ICU utilization patterns described in local and regional cohorts [14, 16, 59]. Longitudinal administrative data from Philadelphia ICUs document a substantial increase in critical care utilization for opioid withdrawal diagnoses coinciding with the medetomidine era. In one study, median quarterly ICU charges for these admissions rose by more than an order of magnitude compared with the pre-medetomidine baseline [59]; in another, nearly 32% of OUD-related hospitalizations involved dexmedetomidine administration in an ICU by the third quarter of 2025 [60].

Onset and Clinical Features

Withdrawal typically begins within 4 to 6 hours of last illicit opioid use, earlier than in traditional opioid or sedative withdrawal syndromes, though some patients present with mild symptoms that progress over 12 to 24 hours [11, 12, 14, 15]. Early features include anxiety, fine tremor without clonus or hyperreflexia, diaphoresis, and the onset of nausea and vomiting. Vomiting quickly becomes a dominant feature and is frequently refractory to typical first line agents such as ondansetron [14, 16]. As withdrawal progresses, patients often develop sinus tachycardia and hypertension; in some instances, these can reach extreme ranges, with reports describing heart rates exceeding 180 beats per minute and systolic blood pressures above 240 mmHg with diastolic pressures above 120 mmHg [14, 16]. A subset develop a distinctive encephalopathy characterized by hypoactive delirium and, in severe cases, hyperthermia and myoclonic jerking/high amplitude tremor, which can mimic fever, sepsis, or seizure [11, 14, 16]. Complications include Posterior Reversible Encephalopathy Syndrome (PRES) attributable to severely elevated blood pressure, non-ST-elevation myocardial infarction consistent with demand ischemia or stress cardiomyopathy, and reduced ejection fraction on echocardiography [14, 16]. Seizures have been reported, but most often with concurrent GABA-agonist withdrawal, and reports are further confounded by local anesthetic adulterants, fluctuating tremor, and encephalopathy; the independent risk appears low [16].

Laboratory findings can include lactic acidosis, hypokalemia, elevated troponin, and QTc prolongation [14, 16, 28]. QTc prolongation in this setting most often improves with resuscitation, control of withdrawal, and correction of metabolic derangements. A retrospective analysis of patients managed with a multimodal α 2-agonist protocol found no episodes of torsades de pointe or clinically significant dysrhythmia, possibly due to the protective effects of persistent tachycardia [61].

Severity Assessment

Severity assessment in medetomidine withdrawal is complicated by the limitations of existing instruments. The Clinical Opiate Withdrawal Scale (COWS) is familiar to many clinicians for assessment of opioid withdrawal severity, and published cohorts report elevated COWS scores in affected patients, with the multicenter Philadelphia series describing a median maximum COWS of 23 [14, 62]. However, COWS systematically underestimates severity in patients with hypoactive delirium, a defining feature of the most severe presentations: patients who are minimally responsive are unable to report pain or anxiety and score lower than their hemodynamic and metabolic derangements warrant [14, 16]. Many institutions also use the Richmond Agitation-Sedation Scale (RASS) to titrate sedative infusions such as dexmedetomidine [63]. The result is a paradox: the sickest patients may appear "less sick" at the bedside than patients in earlier phases of withdrawal [58]. The Withdrawal Assessment Tool-Alpha 2 Agonist (WAT-A2A) has been developed and preliminarily validated for iatrogenic α 2-agonist withdrawal but only in pediatric populations and has not been evaluated for adult medetomidine withdrawal [64].

In the absence of a validated instrument, severity can be tracked using objective signs that guide titration of specific interventions. Heart rate and blood pressure can drive moment-to-moment α 2-agonist dosing, though they should be interpreted alongside other signs of withdrawal rather than in isolation; patients titrated on blood pressure alone are frequently maintained on higher clonidine doses than their clinical picture warrants. Mental status and vomiting drive decisions about airway protection, level of care, and whether oral medications remain feasible. The most predictive variable for a severe course is a prior episode of medetomidine withdrawal requiring ICU admission, which outperforms self-reported volume or frequency of use, though it remains imperfect [16, 65]. Beyond this history, risk also likely rises with local medetomidine prevalence. Prospective validation of a severe-withdrawal risk tool is a research priority.

Distinguishing Medetomidine Withdrawal from Other Syndromes

The rapid tempo of onset, the severity of autonomic activation, and the poor response to GABA-agonist, opioid, and standard antiemetic therapy distinguish medetomidine withdrawal from other diagnoses [14, 16, 28]. Opioid withdrawal typically does not produce the degree of hypertension or tachycardia seen with medetomidine withdrawal, does not typically cause encephalopathy, and responds to opioid agonist therapy. Benzodiazepine and alcohol withdrawal may mimic or complicate medetomidine withdrawal but the former respond to GABA-agonist therapy, whereas medetomidine can sometimes require multiple parenteral sedatives. Stimulant toxicity can produce sympathetic activation but without the temporal association to withdrawal. When the diagnosis is uncertain, use of benzodiazepines is the safest initial

intervention, given the risk of sympathomimetic toxidrome and alcohol/GABAergic withdrawal seizure. Patient report of medetomidine use, local drug prevalence/checking data and standard toxicology screening may also add diagnostic value.

Observation Period and Transition to Withdrawal

A distinctive feature of medetomidine intoxication is that the acute sedation and withdrawal phases may overlap within a single encounter (Fig. 2). Because dexmedetomidine elimination half-life is only 2 to 3 hours, patients monitored for resolution of intoxication can begin to exhibit withdrawal features within hours of arrival, sometimes while still appearing sedated from the original exposure [14, 27]. Early signs of the transition include increasing heart rate (or normalization of bradycardia) and emergence of the withdrawal features described above. Patients who present with prolonged sedation, sinus bradycardia, or hypotension after a suspected overdose should therefore be observed for signs of early withdrawal if not promptly dispositioned. Patients who remain asymptomatic for 6 to 12 hours after exposure are less likely to progress to severe withdrawal, though progression has been observed beyond 24 hours after last use [28]. The duration of observation required to clear this risk remains an important target for prospective study.

Heart rate is a useful marker of this transition but should be interpreted alongside mental status, blood pressure, and ability to tolerate oral intake [14, 28, 65]. Because severe withdrawal can develop rapidly and standard opioid withdrawal medications are ineffective, discharge after apparent resolution of intoxication requires anticipatory guidance, including clear instructions to return for refractory vomiting, persistent tremor, or change in mental status [28].

Management of Medetomidine Withdrawal

Management rests on three principles: early and rapid control of nausea to preserve the oral route, early and aggressive administration of α_2 agonists to address the underlying pathophysiology, and escalation to parenteral dexmedetomidine when symptoms outpace oral therapy [66]. Concurrent management of opioid withdrawal and initiation of medications for opioid use disorder (MOUD) are also essential.

Antiemetic Therapy

Nausea and vomiting are often rate-limiting because they preclude oral administration of α_2 agonists; aggressive control from the earliest recognition of developing withdrawal is therefore prerequisite to any oral regimen [14, 16]. Ondansetron is typically ineffective once vomiting has begun, while experience suggests dopamine antagonists are more useful and frequently require repeat dosing [14, 16, 28]. Their cumulative QTc effect warrants monitoring given the electrolyte derangements and baseline QTc abnormalities common in this population regardless of the rare incidence of dysrhythmia [61]. Scopolamine and trimethobenzamide have been used adjunctively. Agents and routes are summarized in Table 3.

Table 3. Pharmacotherapy for Medetomidine Withdrawal in Hospitalized Patients

Class / Role	Agent	Dose & Route	Key Considerations
Oral α_2 agonist (mainstay)	Clonidine	0.3–0.9 mg PO, repeat q1–2h PRN; titrate to HR/BP	Doses substantially exceed antihypertensive ranges; sublingual absorption preserved if patient cannot swallow; peak oral effect at approximately 1–3 hours, so redosing at the shorter interval requires close HR/BP monitoring to avoid dose stacking
Oral α_2 agonist (adjunct)	Guanfacine	2 mg PO q8h	Useful adjunct; less sedating than tizanidine
Oral α_2 agonist (adjunct)	Tizanidine	2–6 mg PO q8h	Monitor QTc; avoid in pregnancy
Oral α_2 agonist (adjunct)	Lofexidine	0.36–0.72 mg PO	Where available
Transdermal α_2 agonist	Clonidine patch	0.3 mg/24h; up to 3 patches concurrently (replace after 1 week)	Apply early even with initial bradycardia/hypotension if expected to require hospitalization; 18–24h onset aligns with peak withdrawal; facilitates dexmedetomidine weaning
Parenteral α_2 agonist	Dexmedetomidine	1–2 mcg/kg IV bolus → 0.5–1.5 mcg/kg/hr; titrate q15–30 min; up to 2.5 mcg/kg/hr in severe cases	Cornerstone when oral therapy outpaced; 24–72h infusion typical; sinus bradycardia at high doses without other significant adverse effects
Antiemetic – first-line	Prochlorperazine, olanzapine, chlorpromazine, droperidol	IV/IM; repeat dosing common	Ondansetron typically ineffective; monitor QTc – torsades not reported in this context and likely partially protected by severe tachycardia
Antiemetic – adjunct	Scopolamine transdermal; trimethobenzamide IM	1 mg; 150 mg IM	Useful when dopamine antagonists are insufficient
GABA-agonist adjunct	Benzodiazepines, phenobarbital, ketamine	1–2 mg lorazepam IV, 5–10 mg diazepam, 2–4 mg midazolam q1–2 hour PRN; phenobarbital 5–10 mg/kg via short IV infusion can also be considered	Limited monotherapy effect; useful when concurrent GABA-agonist withdrawal present
Concurrent opioid withdrawal management	Methadone	30–40 mg PO first dose; additional 10 mg q4h × 1–3 doses for ongoing symptoms; for IV formulation, use 50% of the PO dose	ECG monitoring given baseline QTc prolongation. Note IV formulation has more significant QTc prolongation than PO.
Concurrent opioid withdrawal management	Hydromorphone IV	1–4 mg q30–60 min, titrated to effect	Bridge while α_2 agonists address medetomidine component, infusions/scheduled doses may be appropriate for patients in ICU settings.
MOUD transition	Buprenorphine (low-dose / microdose induction)	150–450 mcg buccal are common micro-induction doses	Requires 1–5 days to complete
Pre-discharge	Long-acting injectable buprenorphine	Standard dosing	Ensure MOUD continuation at discharge

Doses reflect pooled clinical experience from Philadelphia and Pittsburgh cohorts and are not derived from randomized trials. Protocols vary by institution. HR, heart rate; BP, blood pressure; MOUD, medications for opioid use disorder; PO, by mouth; IV, intravenous; IM, intramuscular; PRN, as needed.

Oral and Transdermal α_2 Agonists

Oral α_2 agonists should be initiated as soon as medetomidine withdrawal is suspected, ideally during the transition from intoxication to withdrawal rather than after symptoms have manifested [14, 16, 28]. Clonidine is the mainstay, dosed above antihypertensive ranges and titrated to heart rate and blood pressure. Guanfacine, tizanidine (with attention to QTc), or lofexidine (inhibited by cost/availability), serve as reasonable second line or adjunctive options [14, 16, 28]. Transdermal clonidine patches can be applied early, even in patients with initial

bradycardia or hypotension, because their 18- to 24-hour onset aligns with the peak of withdrawal and provides baseline α_2 tone that may facilitate eventual weaning from parenteral therapy [14, 67]. Oral clonidine tablets are absorbed sublingually with preserved efficacy when patients cannot swallow, and can be considered before abandoning oral therapy [68].

Given medetomidine's potency, combination regimens using two or more α_2 agonists across oral and transdermal routes are frequently employed. Scheduled plus as-needed dosing maintain α_2 tone during rapid, unpredictable progression; as supplemental requirements subside, scheduled agents are tapered [14, 16, 28]. Agents and initial doses are detailed in Table 3.

α_2 -agonist therapy is increasingly continued beyond the acute phase, with some patients discharged on oral clonidine and some outpatient providers continuing therapy for weeks. This has been prompted by recurrent hypertension and tachycardia with clonidine dose de-escalation and anecdotal reports of an α_2 -specific craving, distinct from opioid craving, that may drive return to use (though it is hard to disentangle from opioid-driven relapse). Philadelphia health department guidance now recommends tapering clonidine during hospitalization to a discharge regimen not exceeding 0.3 mg three times daily, with outpatient follow-up within 2 to 5 days and continued taper over weeks to months [45]. Long-acting injectable α_2 -agonist therapies are potentially vital therapeutic targets.

Parenteral Dexmedetomidine

When vomiting precludes oral administration or multiple oral α_2 agents prove ineffective, parenteral dexmedetomidine becomes the cornerstone of management. Standard bolus and infusion parameters are summarized in Table 3; for refractory cases, rates exceeding the conventional critical-care maximum of 1.5 mcg/kg/hour, and up to 2.5 mcg/kg/hour, have been used safely, though sinus bradycardia without hypoperfusion has been observed; implementation requires interdisciplinary collaboration across medicine, nursing, and pharmacy [14, 28, 66, 69]. Most patients require 24 to 72 hours of infusion. As symptoms improve, overlap with oral and transdermal α_2 agonists allows titration off the infusion and transfer to non-critical-care settings; some institutions have extended dexmedetomidine administration to intermediate-care settings to alleviate ICU demand, though this practice varies and lacks validated titration protocols. Future studies should assess the efficacy and financial impact of this practice.

Other Adjunctive Medications

Benzodiazepines, phenobarbital, and ketamine have limited effect as monotherapy but may augment α_2 -agonist therapy, particularly in patients with concurrent GABA-agonist withdrawal [14, 28, 65]. Sublingual dexmedetomidine, approved for agitation in schizophrenia and bipolar disorder, is dosed too low to be impactful, but merits study given the challenges with oral access [70]. Intranasal dexmedetomidine is similarly limited by volume and concentration constraints.

Concurrent Opioid Management

To date, medetomidine withdrawal has not been observed in isolation of opioid withdrawal, typically from fentanyl. Evidence-based opioid withdrawal management should therefore remain a cornerstone of care and should involve buprenorphine or methadone alongside an α_2 agonist (at doses noted above) and typical non-opioid adjuvants. Because the onset of medetomidine withdrawal often precedes opioid withdrawal, patients who appear to be in moderate-to-severe opioid withdrawal within hours of last use may in fact be exhibiting α_2 -agonist withdrawal; initiation of buprenorphine in this window based on COWS score alone can precipitate opioid withdrawal in a patient who has not yet metabolized residual fentanyl [28]. Consultation with addiction specialists can assist with disentangling these overlapping syndromes in the context of buprenorphine induction.

Short-acting full opioid agonists serve as a bridge for the opioid component while α_2 agonists address the medetomidine component [14, 28, 71], although their efficacy relative to methadone or buprenorphine is unestablished. Low-dose buprenorphine initiation with opioid continuation, using transdermal, transmucosal, or intravenous buprenorphine formulations, may reduce the chance of precipitated withdrawal [14, 72, 73] but requires 1 to 5 days to complete an induction. Methadone is a safe, potent, long-acting, and effective alternative to buprenorphine for opioid withdrawal [74]; induction can proceed immediately, though its pharmacology warrants caution and requires expertise for titration. ECG monitoring should also be considered given baseline QTc prolongation in this population [14, 28, 71]. Hospitals should also establish referral pathways to opioid treatment programs and ensure continuation of MOUD at discharge. Long-acting injectable buprenorphine (LAIB) can be considered before discharge, though it does not treat medetomidine withdrawal [28]; we have seen patients re-present in severe withdrawal despite recent LAIB treatment, further supporting medetomidine withdrawal as a distinct syndrome. Opioid agonist dosing is detailed in Table 3.

These pressures are reflected in practice. Across two Philadelphia emergency departments spanning the xylazine/medetomidine era transition, receipt of any MOUD fell from 46.8% to 27.9%, driven by a decline in buprenorphine uptake from 43.5% to 19.3% (partially offset

by the introduction of methadone) [47]. Whether this reflected clinician reluctance, patient refusal, or difficulty tolerating oral administration while vomiting/encephalopathic cannot be resolved from these data and are target for additional study.

Outpatient and Behavioral Health Center Management of Medetomidine Withdrawal

The assessment and treatment approaches described above are hospital-based, yet many people who use drugs are first encountered, and often managed, outside the hospital. Community and behavioral-health providers have expressed a strong need for guidance adapted to non-hospital settings. Consistent with this, emergency department disposition to another facility, predominantly behavioral and psychiatric settings, fell from 25.1% to 15.0% across the era transition while admissions rose, suggesting increasing difficulty managing this condition outside hospital settings [47].

Several elements of the above can be delivered at ASAM Level 3.5, 3.7, and 4.0 settings with appropriate monitoring, including early and aggressive oral/transdermal antiemetics, oral/transdermal α_2 -agonist therapy titrated to symptom severity or vital signs, and close observation of oral tolerance. Programs that adopt these elements should define clear triggers for transfer to an emergency department, such as intractable vomiting that precludes oral therapy, escalating tachycardia or hypertension, altered mental status, or other rapidly changing or worsening symptoms.

Conversely, behavioral-health programs are increasingly asked to accept patients after emergency-department monitoring. Isolated cases of severe, delayed-onset symptoms make hard delineations impossible. A reasonable threshold is 12 to 24 hours of observation from last use with preserved oral tolerance. Criteria and bidirectional pathways should be agreed upon in advance with local hospitals, accepting that a subset will still decompensate and require transfer back. After parenteral dexmedetomidine, roughly 24 to 48 hours before transfer back is practical depending on ASAM Level, allowing confirmation that rebound symptoms will not recur and that the patient has stabilized on a de-escalating regimen of oral and transdermal therapy.

Post-acute ambulatory management is also emerging as a distinct practice, though published guidance rests on outpatient clinician experience rather than trial data. Health department recommendations include weekly visits with blood-pressure-guided clonidine titration, dose reduction by one half to two thirds when systolic pressure falls below approximately 110 mmHg, addition of guanfacine or tizanidine when symptoms persist at maximal tolerated clonidine doses [45]. Two strategies for concurrent opioid withdrawal have been described in this setting: gradual co-management, in which methadone or buprenorphine is titrated upward while α_2 agonists are given as needed and illicit use declines, and a sequential approach in which patients are induced on long-acting injectable buprenorphine before α_2 -agonist withdrawal is addressed directly [45].

Special Populations

Pregnancy

Pregnant patients exposed to medetomidine-adulterated fentanyl present particular challenges. Untreated maternal withdrawal risks preterm labor, placental abruption, and fetal distress, and the severity of this syndrome raises the stakes of undertreatment. Standard hyperemesis antiemetics are often inadequate, and antihypertensives commonly used in pregnancy address the downstream hemodynamic derangement but not the underlying α_2 deficit [75]. Clonidine has the most human safety data among the α_2 agonists and no established pattern of teratogenicity; guanfacine has less pregnancy-specific data but no evidence of congenital effects [76]. Tizanidine should be avoided where possible given animal toxicity signals, and dexmedetomidine, while lacking teratogenicity signals, has limited human pregnancy data and should be reserved for severe withdrawal [75, 76]. Lorazepam is the preferred benzodiazepine if GABA-agonist adjunct therapy is required, given its lack of active metabolites and shorter half-life [75]. In our view, pregnancy is not a contraindication to aggressive management: the risks of undertreated withdrawal exceed those of appropriately selected pharmacotherapy [75, 76]. Short- and long-term effects on mother and child remain a research priority.

Neonatal and Fetal Exposure

Direct evidence on gestational medetomidine exposure remains limited to a single published case: a postpartum patient with antepartum exposure developed severe withdrawal requiring intensive management, and her neonate developed a withdrawal syndrome the authors characterized as distinct [77]. A 2025 narrative review of perinatal substance exposures places medetomidine among adulterants for which outcome data are absent [75]. The xylazine era remains the closest parallel: a single case of intrauterine exposure described a term neonate with sustained bradycardia, hypertonicity, irritability, inconsolability, and peripheral vasoconstriction over the first 120 hours of life [78], while neonatal outcomes from xylazine otherwise remain almost entirely uncharacterized [79]. Fetal exposure should nonetheless be expected on pharmacologic grounds. Dexmedetomidine has well-documented placental transfer, with maternal-to-fetal indices of

approximately 0.7–0.9, attenuated but not abolished by high lipophilicity and placental retention [80, 81]. Chronic gestational exposure in dependence therefore may produce steady-state fetal concentrations close to maternal ones.

Three implications follow. Like COWS in adults, Finnegan-style neonatal abstinence scoring was designed for opioid withdrawal and may miss the autonomic features prominent in α 2-agonist withdrawal. Iatrogenic neonatal dexmedetomidine withdrawal, well described in the NICU literature, offers a mechanistic template for what to anticipate [82]. And although clonidine has precedent in neonatal opioid withdrawal, no published experience exists with α 2-agonist replacement in medetomidine-exposed neonates; management should be individualized with obstetric, neonatal, and addiction-medicine input. Prospective characterization of medetomidine-exposed pregnancies, including birth weight, gestational age, neonatal cardiovascular and neurobehavioral findings, and longer-term neurodevelopmental outcomes, is an urgent research priority.

Patients with Psychiatric and Infectious Comorbidities

Hospitalized patients with medetomidine withdrawal frequently have concurrent psychiatric disorders (such as depression, bipolar disorder and other forms of psychosis) and infectious complications of injection drug use, including HIV, hepatitis C, bacteremia, endocarditis, and other soft tissue infections. Available cohort data do not suggest that these comorbidities preclude aggressive withdrawal management, and integrated care within the hospital setting often facilitates medical, psychiatric and addiction treatment [14]. Clinicians should be attentive to interactions between antibiotics, psychiatric medications, and other medications metabolized through CYP pathways, though the glucuronidation-based metabolism of dexmedetomidine limits most interactions of concern [19, 34].

Discussion

The emergence of medetomidine as the dominant fentanyl adulterant in Philadelphia, Pittsburgh and several other regions over the past two years has clarified several features of the adulterated opioid supply that were less visible during the xylazine era. We highlight four.

First, medetomidine demonstrates that the clinical consequences of an α 2-agonist adulterant depend on its specific receptor pharmacology, not only on its class. The xylazine era established that α 2-agonist adulterants can produce naloxone-resistant sedation and distinct wound complications, but whether xylazine produces a discrete withdrawal syndrome remains contested: a Philadelphia cohort found no association between xylazine detection and peak systolic blood pressure or heart rate, and found lower odds of ICU admission among patients with xylazine detected [6, 83]. Medetomidine's greater α 2 potency and selectivity compared to xylazine and its imidazoline-receptor activity produce a qualitatively different syndrome: faster onset, more severe autonomic derangement, refractory vomiting, encephalopathy, and frequent need for intravenous dexmedetomidine [14-16, 18, 23]. The practical implication is that each new agent's receptor profile will shape its clinical fingerprint, even among adulterants of the same class.

Second, the increasing national prevalence of medetomidine has not been followed by the same pattern of withdrawal emergence seen in Philadelphia and Pittsburgh, PA. We suggest that withdrawal requires both a threshold prevalence of medetomidine in the local supply and sufficient concentration within the drug itself. Single use may produce intoxication or overdose, but dependence requires serial, consistent exposure. Localities encountering increasing cases of medetomidine intoxication may therefore see withdrawal cases within weeks to months. Further study is required to confirm these hypotheses.

Third, medetomidine withdrawal strains the coordination between behavioral-health and physical-health care. Integrated, hospital-based addiction care has matured over the past fifteen years, but the severity and tempo of this syndrome expose its seams. Even the highest-acuity behavioral health centers are not equipped to manage severe medetomidine withdrawal, yet patients should not be routed uniformly to emergency departments. Assessment and disposition criteria between substance-use and acute-care providers, together with bidirectional transfer pathways, are urgently needed. Compounding this, caring for an unfamiliar, higher-acuity population with a behaviorally challenging syndrome has created tension among patients and staff. Sustaining these encounters requires coordination among behavioral-health and addiction services in physical-health spaces, including the ICU, where such collaboration is historically uncommon. This challenge also creates an opportunity to build treatment spaces designed for collaborative care.

Fourth, and most consequential for health systems, the syndrome strains hospital capacity. A condition now routinely requiring critical care did not exist three years ago, adding patients and cost to systems with little reserve. Durable responses must improve efficiency and reform reimbursement to better support this type of care.

Conclusion

Medetomidine has replaced xylazine as the dominant α 2-agonist adulterant in fentanyl supplies in Pennsylvania and surrounding regions. Its clinical picture differs meaningfully from the xylazine era, with more profound sedation and sinus bradycardia in acute intoxication and a rapidly progressive withdrawal syndrome of severe autonomic dysregulation, intractable vomiting, and encephalopathy. Management differs fundamentally from traditional opioid and sedative withdrawal and requires far more intensive treatment and resources, alongside concurrent management of opioid withdrawal and transition to MOUD. The medetomidine era has exposed the gulf between behavioral-health and physical-health systems and the need for more integrated, coordinated care across the continuum.

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- b. **Conflict of Interest:** KSL, JMP, LCW, DT, PD, MJL, DG, JD, AJK, BH, and APT have nothing to disclose.
- c. **Human and Animal Rights and Informed Consent:** No animal or human subjects were used by the authors in this study, IRB review was not warranted.

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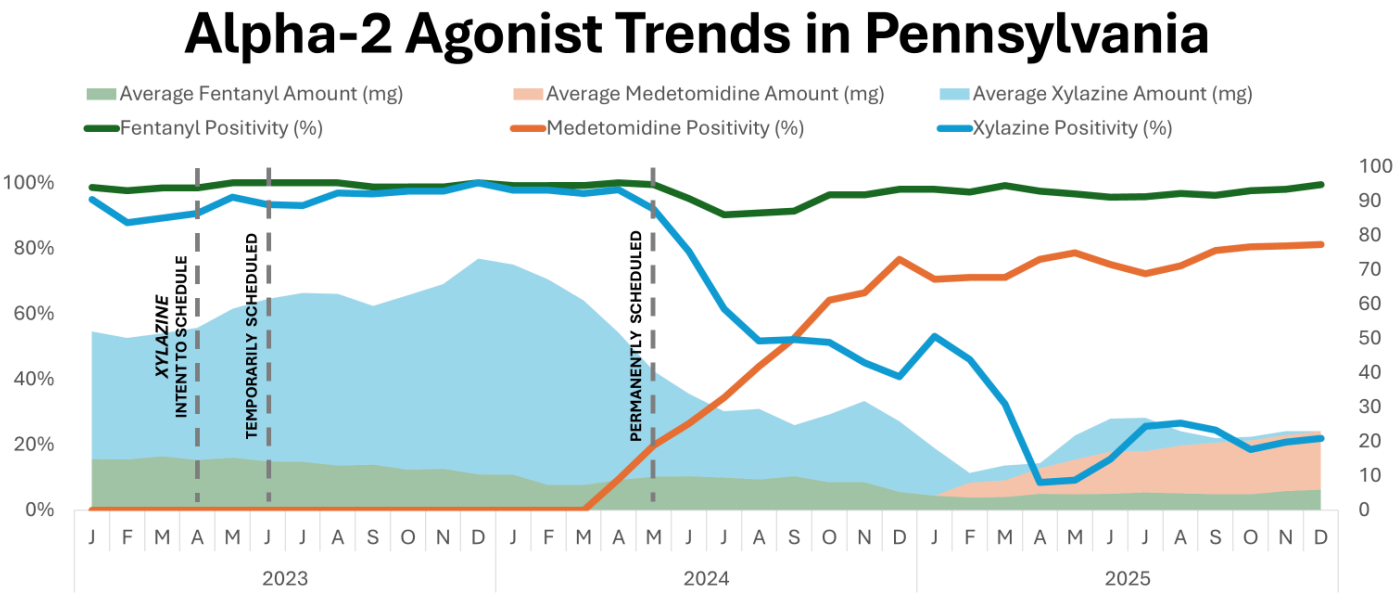
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Figures



Commentary: Leading up to 2023, the prevalence of xylazine in Pennsylvania was increasing, as well as the amount of xylazine in drugs products. In April 2023, Governor Josh Shapiro announced intent to temporary place xylazine as a Schedule III controlled substance, and in June 2023, this order was enacted. Subsequently, the prevalence of xylazine remained unaffected, while the amount of xylazine in drug products continued to increase. The average amount of xylazine in drug products reached its maximum (>60%) in late 2023 to early 2024, before beginning to decline in 2024 thereafter. In the first days of May 2024, our laboratory began detecting medetomidine in drug products, often alongside xylazine. In mid-May 2024, Governor Josh Shapiro signed a bill into law to permanently place xylazine in Schedule III. Since early 2024, xylazine prevalence and amount per drug product have declined while medetomidine prevalence and amount have continually increase. Today, xylazine remains in the drug supply, but at lesser magnitude.

Source: NPS Discovery, Center for Forensic Science Research & Education www.npsdiscovery.org

Figure 1
Alpha-2 agonist trends in Pennsylvania, 2023–2025. Dashed vertical markers denote xylazine's intent-to-schedule, temporary scheduling, and permanent scheduling milestones; medetomidine positivity began rising in early May 2024, before permanent scheduling in mid-May 2024. Source: NPS Discovery, Center for Forensic Science Research and Education.

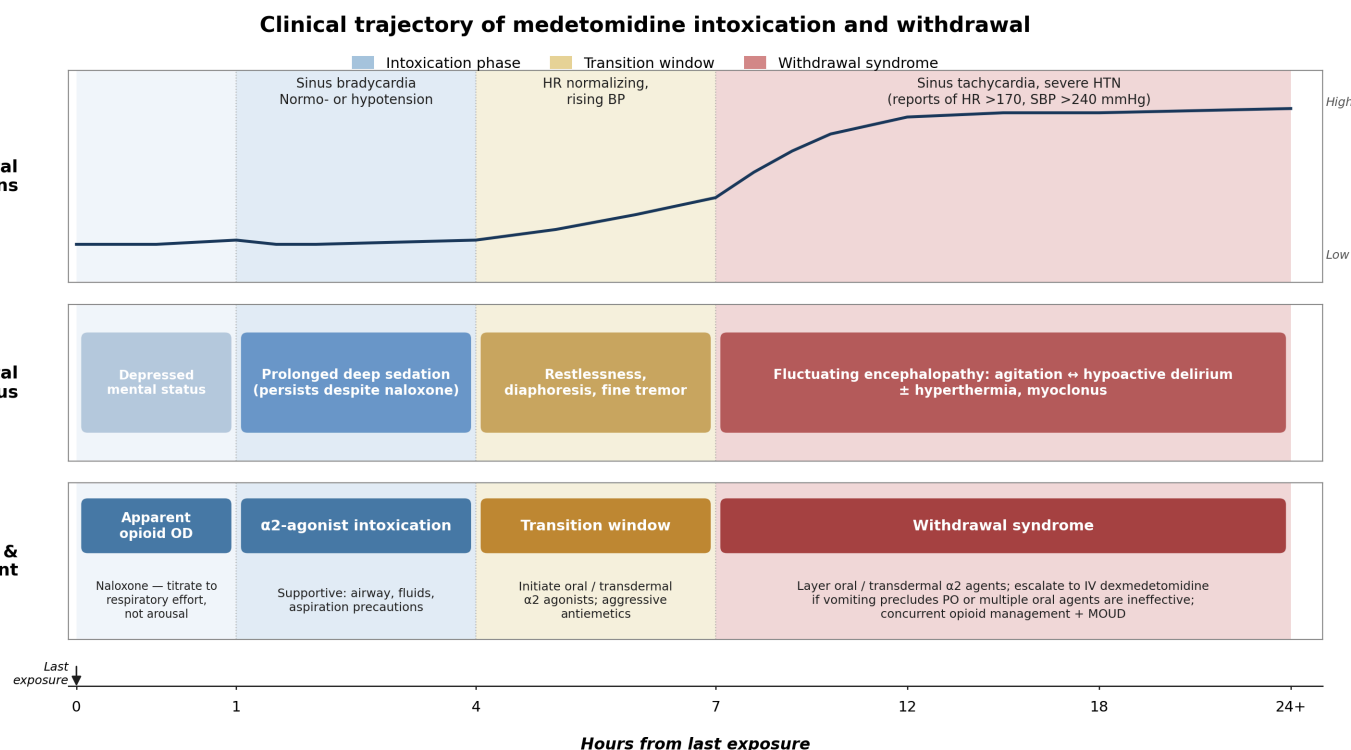


Figure 2

Clinical trajectory of medetomidine exposure and timeline of care needs, from initial exposure and intoxication phases through a crucial transition window, until frank withdrawal sets in and management becomes more complex and higher risk.

Supplementary Files

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