Babies breaking bad: neonatal and iatrogenic withdrawal syndromes

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Purpose of review
This review will summarize the symptoms, evaluation, and treatment of neonatal and iatrogenic withdrawal syndromes.

Recent findings
Buprenorphine is emerging as the drug of choice for maintaining opioid-dependent women during pregnancy, because of its association with less severe withdrawal symptoms. Recent findings suggest it may be the drug of choice for treating the opioid-exposed neonate as well.

Summary
Healthcare workers should be cognizant of the risk factors for neonatal abstinence syndrome (NAS), as well as its symptoms, so that nonpharmalogic and pharmacologic therapies can be initiated. With increased emphasis on pain control in children, it is likely that iatrogenic withdrawal will continue to be a concern, and healthcare workers should understand the similarities and differences between this and NAS.

Keywords
buprenorphine, methadone, neonatal abstinence syndrome, opiate withdrawal

INTRODUCTION

Recent studies have shown an increase in neonatal abstinence syndrome (NAS) over the last decade [1▪]. During the same time period, increased awareness of the need for adequate pain control and sedation in critically ill children resulted in more liberal use of opioids and benzodiazepines, leading to an increased incidence of iatrogenic chemical dependence. These two trends prompt the need to review the identification, management, and prevention of withdrawal syndromes in pediatrics.

The best-described withdrawal syndrome is NAS that occurs after birth, when intrauterine exposure to certain substances is abruptly discontinued. This has been documented for opioids, benzodiazepines, selective serotonin reuptake inhibitors, mood stabilizers, and nicotine [2▪▪,3▪▪]. A similar syndrome occurs when critically ill infants and children develop physical dependence on medications, most commonly opioids and benzodiazepines, used to achieve analgesia and sedation. Withdrawal commonly becomes an issue in critically ill, mechanically ventilated patients who often require prolonged sedation [4]. Inadequate attention to withdrawal can lead to life-threatening complications, patient discomfort, and prolonged hospital stays. The following article serves to review the current literature on prevention, recognition, and management of withdrawal syndromes in pediatrics.

RISK FACTORS

Both human and drug characteristics impact the severity of withdrawal as measured by the length of hospital stay and the need for pharmacologic therapy.

Neonatal withdrawal

In the neonate, gestational age affects the severity of NAS, with milder symptoms developing in premature infants. This is thought to be related to immaturity of the central nervous system, lower fat

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KEY POINTS

- NAS and iatrogenic withdrawal syndrome have similar symptoms.
- Recognition and treatment of opioid withdrawal are confounded by concurrent benzodiazepine withdrawal.
- Assessment of iatrogenic withdrawal remains challenging given the paucity of research beyond the neonatal period.
- Evidence-based clinical guidelines are needed for optimal management of pediatric withdrawal syndromes.

deposits of drug, and decreased total drug exposure [3▪▪,5,6,7▪]. Although Jansson *et al.* [8] found increased symptoms and need for greater pharmacologic therapy in males, multiple other studies found each sex to be equally affected [9,10]. Wachman *et al.* [11] believe that they may have identified a single nucleotide polymorphism that is associated with more severe NAS. Maternal factors predictive of worse neonatal withdrawal symptoms include polysubstance use (opioids and benzodiazepines in particular) [6,12,13▪] and perinatal methadone use, whereas maternal use of buprenorphine (BPH) predicts less severe symptoms [8,14]. Some controversy surrounds whether or not increased maternal methadone dosage is associated with an increased rate or severity of symptoms [13▪,15,16]. It does appear that maternal dose has a positive correlation with length of hospital stay [7▪], but if the mother has not used opioids within 1 week of delivery there is a lower risk of NAS [3▪▪].

Iatrogenic withdrawal

There are multiple risk factors that contribute to the development of iatrogenic withdrawal. Regardless of the medication dose, genetic variations influence individual response to opioid analgesia and development of tolerance [4]. There are also drug-related risk factors that have been identified in children, including rapid tapering or abrupt discontinuation of opioids and benzodiazepines, length of exposure/duration of treatment, and high total cumulative dose [3▪▪,4,14,17–19]. Although data on defining high dose vary, exceeding 5–7 days of therapy has consistently been identified as a risk factor. A recent clinical report published by the American Academy of Pediatrics (AAP) suggests that setting a threshold at 2 mg/kg of fentanyl exposure or 7 days' duration of therapy would predict likelihood of withdrawal to fall between 50–100% [3▪▪,20,21▪]. Keeping these criteria in mind can aid in identifying children at greatest risk of withdrawal, developing assessment tools, and initiating weaning protocols appropriately.

SYMPTOMS

In order to assess, treat, or ideally prevent withdrawal syndromes, it is essential not only to identify risk factors, but also to recognize the symptoms.

Neonatal withdrawal

The timing and features of withdrawal symptoms in NAS depend on the substance. They begin within 24 h of birth for heroin and 2 to 6 days after birth for methadone or BPH. Symptoms of benzodiazepine withdrawal can be delayed a week or more [2▪▪,3▪▪]. The abrupt discontinuation of exogenous opioids results in supra-normal noradrenaline release, which in turn causes autonomic, neurologic, and gastrointestinal symptoms (Table 1) [2▪▪,3▪▪,14,15,17,19,22▪▪,23,24]. The localization of symptoms to these areas is because of the concentration of opioid receptors in the CNS and gastrointestinal tracts. Although the symptoms of opioid withdrawal are largely the same, regardless of the opioid to which the infant was exposed, there have been minor differences noted. Neonates with exposure to methadone have more undisturbed tremors and hyperactive moro reflex compared with neonates with BPH exposure, who have nasal stuffiness, sneezing, and loose stools [25▪].

Iatrogenic withdrawal

Iatrogenic withdrawal develops with abrupt discontinuation of medication after as little as 72 h of exposure [4,21▪] and onset of symptoms occurs most quickly with short-acting opioids like fentanyl. Benzodiazepine withdrawal symptoms can be delayed for a week or more [2▪▪,3▪▪]. Most of the understanding of pediatric withdrawal has been derived from research on intrauterine drug-exposed newborns and opioid-addicted adults [14]. Symptoms of opioid withdrawal are similar in newborns and children [14]; however, unlike in neonates, most critically ill ventilated children receive both opioids and benzodiazepines. The concurrent use of these medications makes it difficult to differentiate the symptoms of one from the other. Research suggests that they have a similar withdrawal profile, perhaps with the exception of gastrointestinal symptoms observed in opioid withdrawal. Major symptoms of benzodiazepine withdrawal in children are included in Table 1. Until recently these

Table 1. Withdrawal symptoms

	Autonomic	Neurologic signs	Gastrointestinal signs
Opioids	Temperature instability	Irritability[a]	Poor feeding
	Low-grade fever	Poor sleep[a]	Poor weight gain
	Diaphoresis	Increased muscle tone	Diarrhea
	Mottling	Tremor[a]	Vomiting
	Piloerection	High-pitched cry	
	Tachypnea	Seizure	
	Nasal stuffiness	Sneezing/yawning	
Benzodiazepines		Muscle twitching	
		Inconsolable crying[a]	
		Grimacing	
		Jitteriness	
		Visual/auditory hallucination	
		Disorientation	
		Seizures	
		Movement disorder[a]	

[a]Indicates presence in combined benzodiazepine and opioid withdrawal.

symptoms have been described on the basis of single case reports and small case series that correspond to studies in adult patients [14]. A recent larger prospective study by Ista *et al.* [19] expanded to include all 24 symptoms of opioid and benzodiazepine withdrawal described in the literature for ICU patients. Unlike previous studies, this study suggested that gastrointestinal symptoms such as vomiting and diarrhea may also be part of benzodiazepine withdrawal [19], making differentiation even more challenging.

ASSESSMENT

In order to optimally treat withdrawal, one must both recognize the symptoms and have an objective-validated reliable tool to measure severity.

Neonatal withdrawal

The majority of research on neonatal withdrawal has used the Finnegan Scale [26], or the modified Finnegan Scale, as these scales were developed in 1975 [27,28] (Table 2). These scales, developed on term and near-term infants, score infant behaviors associated with withdrawal [15]. The infant is evaluated every 4 h and their Finnegan Score is based on behaviors during that period. If the score is greater than or equal to 8 on any three consecutive ratings, the average of two scores is greater than or equal to 12, or the scores for two consecutive ratings are greater than or equal to 12, the infant should be started on pharmacologic therapy [29▪]. A survey of accredited neonatology fellowships showed that only slightly more than half had a written NAS policy, and fewer than three-quarters used a published NAS scoring system [30]. Despite these statistics from accredited training programs, any healthcare organization that serves neonates should adopt a single abstinence scoring form to avoid individual variation in assessment [3▪▪]. Direct instruction and education regarding the scoring sheet improves interrater reliability and decreases subjectivity [29▪,31▪▪]. Infants with known intrauterine exposure should be monitored for at least 72 h.

Iatrogenic withdrawal

Adequate pain control and sedation have caused an increased incidence of tolerance, physical dependence, and subsequent withdrawal mainly from morphine, fentanyl, and midazolam (the most commonly used agents). This is largely observed in critically ill children in the Pediatric Intensive Care Unit (PICU). Studies have suggested that opioid withdrawal occurs in as many as 57% of PICU patients [4,14,18–20,32] and the incidence of benzodiazepine withdrawal ranges from 17–35% depending on the study [14,17,19,33]. Although adequate pain control and sedation are considered essential, the consequences of oversedation include increased time on ventilator support, prolonged PICU stay and overall lengthened hospital course, highlighting the need for balance. Despite this, evidence-based practice guidelines for appropriate

Table 2. Finnegan neonatal abstinence scoring

Systems	Signs and symptoms	Score	AM 2	4	6	8	10	12	PM	4	6	8	10	12	Daily Wt.
Central nervous system disturbances	High-pitched cry	2													
	Continuous high-pitched cry	3													
	Sleeps <1 h after feeding	3													
	Sleeps <2 h after feeding	2													
	Hyperactive moro reflex	2													
	Markedly hyperactive moro reflex	3													
	Mild tremors disturbed	2													
	Moderate severe tremors disturbed	3													
	Mild tremors undisturbed	1													
	Moderate severe tremors undisturbed	2													
	Increased muscletone	2													
	Excoriation (specify area): _____	1													
	Myoclonic jerks	3													
	Generalized convulsions	3													
Metabolic vasomotor/respiratory disturbances	Sweating	1													
	Fever <101°F (39.3°C)	1													
	Fever >101 °F (39.3°C)	2													
	Frequent yawning (>3–4 times/interval)	1													
	Mottling	1													
	Nasal stuffiness	1													
	Sneezing (>3–4 times/interval)	1													
	Nasal flaring	2													
	Respiratory rate >60/min	1													
	Respiration rate >60/min with retractions	2													
Disturbances	Excessive sucking	1													
	Poor feeding	2													
	Regurgitation	2													
	Projectile vomiting	3													
	Loose stools	2													
	Watery stools	3													
Summary	Total score														
	Scorer's initials														
	Status of therapy														

Adapted from [28].

management of analgesia/sedation and withdrawal are lacking and assessment remains challenging.

Most research in iatrogenic withdrawal syndrome relies on tools validated only in the neonate, scoring some clinical findings only observed during the neonatal period, such as the moro reflex, which disappears by 3 months of age, or high-pitched cry [14,34,35]. These scales have limited clinical application given issues with validity, frequency of assessments, and absence of guidelines for pain and sedation management in most PICUs [34]. In addition, during evaluation it is often difficult to differentiate the signs and symptoms of withdrawal from those of illness, inadequate pain control/sedation, or agitation from medical interventions such as mechanical ventilation [19], potentially leading to overdiagnosis of withdrawal.

Multiple assessment tools have been used to score symptom severity in iatrogenic withdrawal syndrome, the newest and most promising being the Withdrawal Assessment Tool (WAT-1) and the Sophia Observation Withdrawal Symptoms-scale (SOS). Franck *et al.* [24,35,36▪] developed and studied the WAT-1 during a prospective study in two University-affiliated PICUs enrolling children weaning from more than 5 days of continuous opioid and benzodiazepine infusions. It examined 19 withdrawal symptoms derived from the Opioid Benzodiazepine Withdrawal Scale (OBWS), previously the only tool with prospective validation in PICU patients, in combination with literature review and expert opinion. This study suggested that the WAT-1 was superior to the OBWS, demonstrating improved sensitivity in detecting withdrawal symptoms (87% as compared with 50%) and a specificity of 88%, when using a score of greater than or equal to 3 to define significant withdrawal [24,35] (Table 3). Later Franck *et al.* [24] performed a similar study expanded to include 22 PICUs to support validity, reliability, and generalizability of the WAT-1 in measuring iatrogenic withdrawal. The authors confirmed their previous findings. Although WAT-1 has advantages over previous tools in that it is simpler and less time consuming to use, it is limited in that the scale lacks symptoms specific to benzodiazepine withdrawal, making it better in identifying withdrawal from opioids. Additionally, both studies were confounded by polypharmacy, with 39% of patients in the initial study receiving one to three nonopioid/nonbenzodiazepine medications [24,35].

Investigations by Ista *et al.* used the self-developed Sophia Benzodiazepine Opioid Withdrawal Checklist (SBOWC) to expand from previous studies and include all withdrawal symptoms from benzodiazepines and opioids described in the literature [19,34,36▪]. This prospective, repeated measures study included children who received greater than or equal to 5 days of continuous IV opioid and/or benzodiazepine infusion [19,34] and used the SBOWC as the basis for constructing the SOS to monitor iatrogenic withdrawal symptoms in PICU patients [23]. The prevalence of withdrawal syndromes in this study correlated with previous scales; however, almost 75% of the patients were infants, suggesting that the symptoms may not necessarily apply to older children [19,34]. As the SOS included more benzodiazepine withdrawal symptoms than the WAT-1, the authors concluded that this tool was a more sensitive scale for detecting benzodiazepine withdrawal [23]. Because most PICUs utilize both opioids and benzodiazepines simultaneously in their intubated patients, the SOS may offer an advantage over the WAT-1 once cut-off scores, sensitivity, and specificity are delineated, an important factor given the different treatment.

MANAGEMENT

The management techniques used to resolve withdrawal symptoms depend in part on the substance use that led to the withdrawal and in part on the age and circumstance of the patient.

Neonatal withdrawal

The goal of the therapy is to relieve signs of withdrawal and to prevent complications such as fever, weight loss, and seizures [3▪▪]. Although between 50 and 95% of all opioid-exposed infants require pharmacologic therapy [15], nonpharmacologic strategies exist that have been found to decrease signs and symptoms of NAS. Swaddling, gentle handling, decreasing noise, and minimizing overhead lights have all been shown to be beneficial in symptom reduction by limiting external stimulation [3▪▪,15,29▪,36▪]. The utilization of frequent, small, hypercaloric feeds (24 kcal/oz) has been shown to minimize weight loss [3▪▪,15]. Interestingly, although absorption of methadone through breast milk is minimal, breastfeeding by mothers on methadone has been found to minimize NAS symptoms [3▪▪,7▪,13▪,34,37,38]. It should be noted that breastfeeding is only to be encouraged among mothers whose drug use is limited to methadone or BPH. Use of illicit drugs is a contraindication for breastfeeding. Although no current research documents the efficacy of acupuncture in the treatment of NAS, one study did find active points in infants with withdrawal symptoms [39]. These active points may be sites for intervention in future studies. Wherever possible, it is important that the parents

Table 3. Withdrawal Assessment Tool-1 (WAT-1)

WITHDRAWAL ASSESSMENT TOOL VERSION 1 (WAT – 1)

Patient Identifier														
	Date:													
	Time:													
Information from patient record, previous 12 hours														
Any loose /watery stools	No = 0 Yes = 1													
Any vomiting/wretching/gagging	No = 0 Yes = 1													
Temperature > 37.8°C	No = 0 Yes = 1													
2 minute pre-stimulus observation														
State	SBS[1] ≤ 0 or asleep/awake/calm = 0 SBS[1] ≥ +1 or awake/distressed = 1													
Tremor	None/mild = 0 Moderate/severe = 1													
Any sweating	No = 0 Yes = 1													
Uncoordinated/repetitive movement	None/mild = 0 Moderate/severe = 1													
Yawning or sneezing	None or 1 = 0 ≥2 = 1													
1 minute stimulus observation														
Startle to touch	None/mild = 0 Moderate/severe = 1													
Muscle tone	Normal = 0 Increased = 1													
Post-stimulus recovery														
Time to gain calm state (SBS[1] ≤ 0)	< 2min = 0 2 - 5min = 1 > 5 min = 2													
Total Score (0-12)														

WITHDRAWAL ASSESSMENT TOOL (WAT – 1) INSTRUCTIONS

- Start WAT-1 scoring from the **first day of weaning** in patients who have received opioids +/or benzodiazepines by infusion or regular dosing for prolonged periods (e.g., > 5 days). Continue twice daily scoring until 72 hours after the last dose.
- The Withdrawal Assessment Tool (WAT-1) should be completed along with the SBS[1] at least once per 12 hour shift (e.g., at 08:00 and 20:00 ± 2 hours). The progressive stimulus used in the SBS[1] assessment provides a standard stimulus for observing signs of withdrawal.

Obtain information from patient record (this can be done before or after the stimulus):

- ✓ **Loose/watery stools**: Score 1 if any loose or watery stools were documented in the past 12 hours; score 0 if none were noted.
- ✓ **Vomiting/wretching/gagging**: Score 1 if any vomiting or spontaneous wretching or gagging were documented in the past 12 hours; score 0 if none were noted
- ✓ **Temperature > 37.8°C**: Score 1 if the modal (most frequently occurring) temperature documented was greater than 37.8 °C in the past 12 hours; score 0 if this was not the case.

2 minute pre-stimulus observation:

- ✓ **State**: Score 1 if awake and distress (SBS[1]: ≥ +1) observed during the 2 minutes prior to the stimulus; score 0 if asleep or awake and calm/cooperative (SBS[1] ≤ 0).
- ✓ **Tremor**: Score 1 if moderate to severe tremor observed during the 2 minutes prior to the stimulus; score 0 if no tremor (or only minor, intermittent tremor).
- ✓ **Sweating**: Score 1 if any sweating during the 2 minutes prior to the stimulus; score 0 if no sweating noted.
- ✓ **Uncoordinated/repetitive movements**: Score 1 if moderate to severe uncoordinated or repetitive movements such as head turning, leg or arm flailing or torso arching observed during the 2 minutes prior to the stimulus; score 0 if no (or only mild) uncoordinated or repetitive movements.
- ✓ **Yawning or sneezing** > 1: Score 1 if more than 1 yawn or sneeze observed during the 2 minutes prior to the stimulus; score 0 if 0 to 1 yawn or sneeze.

1 minute stimulus observation:

- ✓ **Startle to touch**: Score 1 if moderate to severe startle occurs when touched during the stimulus; score 0 if none (or mild).
- ✓ **Muscle tone**: Score 1 if tone increased during the stimulus; score 0 if normal.

Post-stimulus recovery:

- ✓ **Time to gain calm state** (SBS[1] ≤ 0): Score 2 if it takes greater than 5 minutes following stimulus; score 1 if achieved within 2 to 5 minutes; score 0 if achieved in less than 2 minutes.

Sum the 11 numbers in the column for the total WAT-1 score (0-12).

[1]Curley et al. State behavioral scale: A sedation assessment instrument for infants and young children supported on mechanical ventilation. Pediatr Crit Care Med 2006;7(2):107-114.

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and family be encouraged to actively participate in management of NAS, to promote bonding between parent and child and to provide opportunity to observe interactions assessing for social risks and safety [29▪].

There have been many studies evaluating single and multidrug therapies for NAS [40,41]. Multiple sources identify opioid replacement as the ideal treatment for opioid withdrawal [3▪▪,15,40–42], finding that it improves weight gain. However, it increases length of stay when compared with nonpharmacologic interventions [41]. The most common single agent in use is oral morphine, which is initiated when infants score greater than or equal to 8 on three consecutive Finnegan ratings [29▪,36▪]. Although some research institutions used a fixed dosing for each range of scores, most utilize weight-based dosing [2▪▪,29▪]. Tincture of opium and paregoric are no longer recommended in neonates, as they have high alcohol content and other additives including camphor, which are not well tolerated in infants [15,29▪].

Methadone and BPH are also options for the first-line treatment of NAS. In most studies, BPH showed benefit over methadone for length of treatment and length of hospital stay [43]. Other benefits include a ceiling effect for respiratory depression, and less cardiovascular lability than methadone [43]. Interestingly, the serum concentration of BPH required for amelioration of symptoms in neonates is significantly less than that required for adults [43].

With all of the above opioid replacement therapies, it is sometimes necessary to add an additional agent (Table 4) [2▪▪,15,29▪,36▪,43–45]. Usually this occurs when the infant continues to show signs of withdrawal despite escalation of the primary therapy to maximal well tolerated dosing [2▪▪]. The most common adjunctive therapy is phenobarbital. It has been found to be useful in controlling the hyperactive symptoms of withdrawal, but ineffective in managing the gastrointestinal symptoms [15]. A recent Cochrane Review concluded that phenobarbital was better than diazepam as an adjunct, particularly if there has been multidrug exposure [40]. There is some concern about the neurodevelopmental effects of phenobarbital on the neonate, which may be addressed in the

Table 4. Pharmacologic therapy for neonatal abstinence syndrome

Drug	Initial dosing	Dosing increases	Rescue dosing	Add adjuvant therapy	Weaning schedule
Morphine	0.1 mg kg^{-1} $dose^{-1}$ orally every 4 h	Increase by 20–30% every 12 h until scores $<8 \times 24$ h	Repeat previous dose between scheduled dose intervals	At morphine dose of 1.25 mg kg^{-1} $dose^{-1}$, add phenobarbital or clonidine	Decrease by 10% every 24 h, while scores <8. Discontinue when 0.15 mg kg^{-1} $dose^{-1}$
Methadone	0.1 mg kg^{-1} $dose^{-1}$ orally every 12 h	Calculate entire methadone dose for previous 24 h and divide by two for BID dosing	Additional dosing of 0.025 mg kg^{-1} $dose^{-1}$every 4 h while scoring >8. Max dose 0.5 mg kg^{-1} $dose^{-1}$	When max dosing has been reached	Decrease by 10% every 1–2 weeks. Discontinue when 0.05 mg kg^{-1} $dose^{-1}$
Buprenorphine	15.9 mcg kg^{-1} $dose^{-1}$ divided in three doses, orally	Increase by 25%	Max dose 60 mcg kg^{-1} $dose^{-1}$		After 3 days of stabilization, decrease by 10% while scores <8. Discontinue when dose is 10% of initial dose
Phenobarbital	20 mg/kg loading	Maintenance dose 5 mg/kg		Adjuvant	
Clonidine	0.5 to 1.5 mcg/kg orally	Increase by over 1 to 2 days to target dose, 3 to 5 mcg kg^{-1} day^{-1}, divided every 4–6 h		Adjuvant	No taper required

max, maximum.

Prophylactic Phenobarbital After Neonatal Seizures trial, due to end in 2014 [2▪▪]. Both phenobarbital and diazepam have been trialed as first-line therapy; neither was as effective as an opioid [41].

Clonidine has also shown utility as an adjunctive therapy. When combined with an opioid, it decreases the length of treatment [29▪,46] and reduces morphine dosages required for neonates exposed to heroin or methadone. Studies showed an increased rate of rebound, but a shorter course of treatment overall. At this time, there are no published studies regarding the use of clonidine and BPH.

Two medications not recommended in the management of NAS are chlorpromazine and naloxone [15]. Although helpful in controlling the gastrointestinal and CNS effects of withdrawal, chlorpromazine has many side effects, including decreased seizure threshold and cerebellar dysfunction [15]. Naloxone in the drug-exposed neonate can be life-threatening by precipitating acute withdrawal and seizure activity.

Although much of the current research in pharmacotherapy for NAS uses the compounds described above, there are novel strategies being considered such as targeting serotonergic pathways, developing immunotherapies, using vaccines and antibodies, and further investigating pharmacogenomics [47▪]. These novel approaches may prove safer and have better outcomes than the traditional therapies for NAS.

Iatrogenic withdrawal

Recognizing the dearth of guidelines for the management of iatrogenic withdrawal, The United Kingdom Paediatric Intensive Care Society, Analgesia and Neuromuscular Blockade Working Group published multidisciplinary consensus guidelines to help establish consistency in analgesia and sedation practices for critically ill children [33]. This was followed in 2012 by a clinical report published by the AAP recommending reasonable practices based on available evidence to help predict and manage acquired opioid and benzodiazepine dependency [3▪▪]. Both reports cite a lack of high-quality evidence to support recommendations, and thus there is still no optimal regimen for treatment of pediatric iatrogenic withdrawal.

Methadone is the most common agent used to treat opioid withdrawal in children given its good bioavailability and long half-life allowing for extended dosing intervals. There are a number of weaning protocols available, each with variations in dosages, weaning increments, and length of the weaning period. In a prospective, double-blind, randomized trial of patients who received fentanyl with or without benzodiazepine infusion for greater than or equal to 5 days, Bowens *et al.* [32] found no advantage of high-dose over low-dose methadone in successfully completing a 10-day taper regardless of total dose or length of fentanyl therapy. Unfortunately, the results were confounded by concurrent benzodiazepine withdrawal and by use of a non-validated assessment tool. In addition, 42% of patients enrolled in the study failed to complete the taper because of deviations from protocol. Another small study looking at a similar population found no difference in withdrawal symptoms between five and 10-day weaning protocols [36▪]. The optimal rate of methadone tapering is not clear, with one study reducing doses 10–20% daily depending on length of wean resulting in an 87% incidence of withdrawal symptoms [14,36▪]. Five to 10% incremental reductions are typical in adult patients [14]. Perhaps the key is not the details of the protocol, but adherence to a single protocol.

Given the prevalence of withdrawal in the PICU, a structured strategy for therapy is needed. Reasonable practices based on available evidence outlined in the AAP clinical report [3▪▪] include: establishment of weaning protocols, based on likelihood of drug dependence, which are initiated when certain dosage thresholds are exceeded. Medications can be tapered rapidly over 24 to 48 h if the defined threshold has not been surpassed, as there is decreased likelihood of withdrawal in these patients; selection of a standardized rescue protocol for withdrawal symptoms that guides conversion to methadone and lorazepam [36▪], one example outlined in Table 5 [3▪▪,20]. Use of such protocols has been shown to decrease total duration of methadone therapy [20] and incidence of withdrawal symptoms [36▪]. Interestingly, recent literature suggests that even when guidelines are in place practitioners may not consistently follow them [21▪]; adoption of the idea that 80% of children can successfully be weaned from methadone in 5–10 days and that the duration of benzodiazepine wean should be proportional to the days of therapy; selection of one assessment tool to be used consistently in monitoring patients for signs and symptoms of withdrawal; adoption of a policy to observe young children for signs and symptoms of withdrawal for 24–48 h after discontinuation of opioid therapy; recognition that use of clonidine, chloral hydrate, or low-dose naloxone infusion [48] has not been proven to reduce withdrawal. One small case series suggests that transdermal clonidine may be useful in prevention of opioid withdrawal [49] with additional limited evidence to suggest dexmedetomidine may play a similar role [50]. However, both

Table 5. Sample weaning protocols

Conversion from 7–14 days of continuous IV fentanyl to oral methadone

Initial dose	Day 2	Day 3	Day 4	Day 5	Day 6
1. Calculate 24-h dose by using current hourly rate.	Give 80% of original daily dose, in three divided doses, Q8h.	Give 60% of original dose, in three divided doses, Q8h.	Give 40% of original dose, in two divided doses, Q12h.	Give 20% of original dose, in one dose.	Discontinue methadone.
2. Calculate equipotent methadone dose by ×100.					
3. Divide by 6 to account for longer half-life, to get total methadone daily dose. Give in four divided doses, Q6h.					

Conversion from >7 days of continuous IV midazolam to oral lorazepam

Initial dose	Day 2	Day 3	Subsequent days
1. Calculate 24-h dose by using current hourly rate.	Decrease by 10–20%, in four divided doses, Q6h.	Decrease by 10–20%, in four divided doses, Q6h.	Continue to decrease by 10–20% daily, then extend dosing interval to Q8h, then Q12 h, then Q24h then Q48h.
2. Account for differences in potency and half-life by ×12 to get total daily lorazepam dose.			Discontinue lorazepam.
3. Give in four divided doses, Q6h.			

alpha 2 agonists can themselves cause withdrawal, possibly limiting their utility.

PREVENTION

It is important to remember that fetal exposure to opioids can occur when the mother is addicted to either prescription or illicit opioids, or required opioids for the management of another disease process, or is maintained on an opioid agent to facilitate well-tolerated withdrawal from addiction [31▪▪]. Although abrupt cessation of drug use during pregnancy is not recommended, there are maternal behaviors that diminish the likelihood or severity of NAS. The risk of complications from illicit opioid use in pregnancy is significant, and pregnant women should be assisted in the transition to a substitute for heroin. If the mother already receives substitutive maintenance therapy, there is data to support BPH over methadone, and either is preferable to morphine [51]. Infants born to mothers on morphine maintenance tend to have quicker-onset withdrawal and worse NAS symptoms [51]. The MOTHER study, a large multicenter randomly controlled trial of mothers on opioid therapy, has contributed a great deal to our understanding of NAS [52]. Infants born to mothers on BPH maintenance therapy (BMT) or methadone maintenance therapy (MMT), had the same percentage of infants requiring treatment, but the infants born to mothers on BMT had higher birth weights [53], required less morphine and had shorter hospital stays than their counterparts on MMT [52,53]. Unfortunately, there was also a higher rate of drop out for mothers in the BMT group when compared with the MMT group, likely due to the decreased opioid effect of BPH [52]. Given that concurrent benzodiazepine use is associated with prolonged length of stay and complicates scoring withdrawal symptoms in NAS, mothers should be counseled to discontinue use during pregnancy [6,12].

CONCLUSION

Neonatal and iatrogenic withdrawal syndromes are complex problems for which simple solutions do not exist. Despite a high incidence of withdrawal in critically ill PICU patients and increased occurrence of NAS, strong evidence-based guidelines do not exist to guide therapy. A consistent approach to assessment and treatment is key, including the following components: refinement of a practical tool for identification of withdrawal symptoms that is simple, efficient, and possesses strong interrater reliability; development of a structured weaning protocol based on clinical evidence;1; and production of new pharmacologic agents targeted at the pathophysiology and symptomatology of withdrawal.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ▪ of special interest
- ▪▪ of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 548).

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