in discomfort, prolonged hospital and PICU stay, and increased morbidity. Treatment options are focused on prevention and/or treatment of symptoms. Prevention is the initiation of medications in order to avoid the onset of symptoms; treatment is the initiation of medications in order to address symptoms of withdrawal when they occur. Although these approaches are similar, it is important to differentiate between these 2 indications because some medications have been studied only to prevent iatrogenic drug withdrawal and may not be the most appropriate choice to initiate for treatment of withdrawal.

The aim of this review is to identify updated prevention and treatment recommendations for opioid and dexmedetomidine withdrawal and to highlight considerations for validated assessment tools for iatrogenic drug withdrawal.

Prevention and Treatment of Opioid Withdrawal

Iatrogenic opioid drug withdrawal or iatrogenic opioid abstinence syndrome (IOAS) occurs in 35% to 57% of children in the PICU upon abrupt discontinuation of opioid continuous infusions. The mechanism of IOAS is believed to be the result of superactivation of adenylate cyclase, coupling of the opioid receptor with G-stimulatory proteins, and activation of excitatory amino acids. Children with IOAS experience withdrawal symptoms from 3 different categories of systems: central nervous system (CNS) irritability (eg, anxiety, agitation, sleep disturbance), gastrointestinal (GI) dysfunction (eg, vomiting, diarrhea), and autonomic dysfunction (eg, tachypnea, diaphoresis, hypertension). However, some patients have experienced other significant symptoms, including myocardial ischemia.
Risk factors for IOAS include cumulative opioid exposure and duration, use of extracorporeal membrane oxygenation, and concomitant neuromuscular blocker infusions. Katz et al performed a prospective, observational study in 23 children receiving fentanyl infusions to identify risk factors for withdrawal based on the cumulative dose and duration. The investigators noted that children receiving 1.5 mg/kg or more of fentanyl or a duration of longer than 5 days had a 50% risk of developing withdrawal, and children receiving 2.5 mg/kg or more or a duration of 9 days or longer had a 100% risk of developing withdrawal. These data suggest that children with less cumulative exposure and a fentanyl infusion duration less than 5 days are at less risk of withdrawal. However, clinicians must be cautious with extrapolating these generalizations to children receiving morphine or hydromorphone infusions, because fentanyl and other synthetic, short-acting opioids have a higher incidence of tolerance and withdrawal than morphine and hydromorphone.

Several sources provide recommendations for prevention and treatment of opioid withdrawal. However, these sources do not provide recommendations based on opioid duration and exposure, and it is plausible that different strategies are needed based on these factors. Table 1 provides recommendations for prevention and treatment of IOAS for children with low risk and high risk for withdrawal.

Several options can be used to prevent IOAS in low-risk patients. One option is to taper their opioid infusion by 10% to 15% every 6 to 8 hours until discontinued. Second, clinicians could discontinue the opioid infusion, monitor for signs of withdrawal, and administer intravenous opioids (eg, morphine or hydromorphone) for breakthrough symptoms. A third option for low-risk patients is to discontinue the opioid infusion, initiate a propofol or dexmedetomidine infusion to facilitate extubation and allow the opioid infusion to wash out of the child’s system, and administer intravenous opioids if needed for breakthrough symptoms. A few

<table>
<thead>
<tr>
<th>Table 1. Approach to Prevention and Treatment of Opioid Withdrawal</th>
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<tbody>
<tr>
<td><strong>Risk Level</strong></td>
</tr>
<tr>
<td>Low risk*</td>
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<tr>
<td></td>
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<tr>
<td></td>
</tr>
<tr>
<td>High risk*</td>
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</tbody>
</table>

*Low-risk patients include children with <1.5 mg/kg or <5 days of fentanyl infusion exposure.

*High-risk patients include children with ≥1.5 mg/kg or ≥5 days of fentanyl infusion exposure.

Data from Johnson, Katz et al, and Tobias.
reports have evaluated the latter approach and have shown positive results, but none of the reports in the PICU have been prospective studies.\textsuperscript{15-18}

A number of options can be implemented to prevent and treat IOAS in high risk children. Clinicians could taper their infusions by 10\% to 15\% every 6 to 8 hours until discontinued. However, this approach may be limited as it could prolong PICU length of stay and increase the risk of other complications, such as central line-associated bloodstream infections.\textsuperscript{19}

The most studied and most practical approach to high-risk patients is to administer another opioid via the IV, transdermal, or enteral route and taper this treatment over a period of days to weeks. It is best to initiate this opioid prior to discontinuation of the child’s current opioid infusion to ensure achievement of a steady-state concentration of the new opioid. First, children could be initiated on intermittent dosing of IV opioids, but this option could be associated with complications similar to those of tapering off IV opioid infusions. Another approach could be to initiate a fentanyl or buprenorphine transdermal patch. This approach may be attractive for children who are unable to take anything enterally. No studies have evaluated buprenorphine for prevention of IOAS. However, Johnson et al\textsuperscript{20} retrospectively evaluated the use of transdermal fentanyl patches to prevent IOAS in 15 children, ages 0.3 to 17 years. Children in this study were initiated on a fentanyl patch that was nearest to their equivalent fentanyl infusion in micrograms per kilogram of body weight per hour (\(\mu g/kg/h\)) just prior to discontinuation. In order to provide the equivalent fentanyl dose, eight (53.3\%) had their transdermal fentanyl patch partially covered with Tegaderm (3M Skin Health, St. Paul, MN) to provide a fraction of the patch an equivalent dose of their fentanyl infusion. It is important to note that the conversion from the fentanyl infusion to patch did not take into account differences in absorption between infants and adolescents, and it is well known that children less than 1 year of age have enhanced absorption of topical medications due to a thinner stratum corneum and increased ratio of skin surface area to body weight.\textsuperscript{19,21}

There were no difference in the number of children who had IOAS symptoms between those with whole versus partially covered patches (\(p >0.05\)). However, the investigators noted a significantly high percentage of children with withdrawal symptoms in this study with fentanyl patches compared with other studies utilizing enteral methadone, 46.7\% versus 30\%.\textsuperscript{22} The investigators also found that most children required IV breakthrough opioids for withdrawal symptoms during the first 5 days of transdermal fentanyl. These data suggest altered transdermal fentanyl absorption, and thus the routine use of transdermal fentanyl to prevent withdrawal should be limited.

The most common approach to prevention of IOAS is initiation of enteral opioids. Short-acting opioids, such as buprenorphine, and immediate-release morphine, oxycodone, and hydromorphone may be used. However, depending on the age of the child and the agent itself, these agents would have to be administered every 3 to 8 hours to control symptoms. Two studies reported positive findings when using buprenorphine for neonates with neonatal abstinence syndrome (NAS), but no studies to date have evaluated this agent for IOAS.\textsuperscript{23,24} Long-acting opioids are generally preferred because they require less frequent administration than short-acting agents. Available long-acting agents include methadone and extended-release formulations of oxycodone, hydromorphone, and morphine. However, methadone is the only one of these available as an oral liquid formulation and would have the most predictable pharmacokinetic profile when administered through a feeding tube. In addition, methadone is an \(N\)-methyl-D-aspartic acid (NMDA) receptor antagonist, and antagonism of the NMDA receptor has been associated with decreased development of opioid tolerance and severity of IOAS symptoms.\textsuperscript{14,22}

Thirteen studies have evaluated the use of methadone to prevent or treat opioid withdrawal.\textsuperscript{25-37} The majority of these studies
have evaluated the use of a formula-based or weight-based approach to determine the initial methadone dose. The formula-based and weight-based dosing strategies were calculated based on pharmacokinetic and equianalgesic parameters or based on the patient’s weight, respectively. Some studies have found that methadone may be more potent than many equianalgesic conversion tables reflect. Further, these equianalgesic conversions are based on data in healthy adults, and thus they would not reflect the pharmacokinetic profile in critically ill children who may have renal and/or hepatic failure, resulting in prolonged half-lives compared with healthy adults.

Table 2 provides an overview of the variability in the methadone dose, interval, and dosage formulation for a 5-kg infant receiving a weight-based or formula-based approach using the dosing strategies found in 10 published studies where the dosing scheme was described. A 12-fold difference in the initial methadone dose between the approaches was described, ranging from 0.05 to 0.6 mg/kg every 6 to 12 hours. Johnson et al conducted a systematic review including 8 reports that described children receiving weight-based and formula-based approaches. The investigators noted that one-third of the patients who were evaluated experienced withdrawal symptoms, and there was no difference among the different strategies. Since many children initiated on methadone for IOAS do not have an ongoing source of pain, the use of an equianalgesic dose is likely excessive. Given the significant variability in selection of a methadone dose in Table 2, use of formula-based approaches can lead to an increased risk of adverse events. One study evaluating the initial methadone dosing found that 10.9% of children had oversedation and required a reduction in their formula-based

### Table 2. Initial Methadone Dosing Regimen for 5-kg Patient Receiving a Fentanyl Infusion With a Current Rate of 5 μg/kg/h and a Total Duration of 9 Days of Fentanyl

<table>
<thead>
<tr>
<th>Initial Dosing Strategy</th>
<th>Examples of Dosing Calculations</th>
<th>Initial Methadone Dosing Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight-based (Tobias 1990)</td>
<td>0.1 mg/kg per dose x 5 kg = 0.5 mg per dose</td>
<td>0.5 mg PO (0.1 mg/kg) every 12 hours</td>
</tr>
<tr>
<td>Weight-based (Tobias 1994, Tobias 1995)</td>
<td>0.05 mg/kg per dose x 5 kg = 0.25 mg per dose</td>
<td>0.25 mg PO (0.05 mg/kg per dose) every 12 hours</td>
</tr>
<tr>
<td>Weight-based (Lugo 2001, Bowens 2011, Steineck 2014)</td>
<td>0.1 mg/kg per dose x 5 kg = 0.5 mg per dose</td>
<td>0.5 mg PO (0.1 mg/kg per dose) every 6 hours</td>
</tr>
<tr>
<td>Formula-based (Robertson 2000)</td>
<td>5 μg/kg/h x 5 kg = 25 mg/h; 0.001 mg/kg x 0.1 mg/kg x 0.25 mg; solve for x = 2.5 mg</td>
<td>2.5 mg IV (0.5 mg/kg per dose) every 6 hours</td>
</tr>
<tr>
<td>Formula-based (Siddappa 2003)</td>
<td>5 μg/kg/h x 5 kg x 24 h x 3 = 1800 μg/d; (1800 μg/d)/(3 doses/d) = 600 μg per dose</td>
<td>0.6 mg IV (0.1 mg/kg per dose) every 8 hours</td>
</tr>
<tr>
<td>Formula-based (Meyer 2001)</td>
<td>5 μg/kg/h x 5 kg = 25 μg/h; 25 μg/h x 60 = 1.5 mg IV morphine; methadone = 1.5 mg IV morphine x 2 = 3 mg</td>
<td>3 mg PO (0.6 mg/kg per dose) every 12 hours</td>
</tr>
<tr>
<td>Formula-based (Bowens 2011)</td>
<td>0.1 mg/kg x 5 kg x 5 μg/kg/h = 2.5 mg</td>
<td>2.5 mg PO (0.5 mg/kg per dose) every 6 hours</td>
</tr>
<tr>
<td>Formula-based (Srinivasan, 2017)</td>
<td>5 μg/kg/h x 24 = 1200 μg/d; 2.5 mg IV methadone = 1 mg IV fentanyl; 2.5 x 1200 μg/d = 3000 μg/d in 2 divided doses</td>
<td>1.5 mg PO (0.3 mg/kg per dose) every 12 hours</td>
</tr>
</tbody>
</table>

Data from Tobias et al, Lugo et al, Robertson et al, Siddappa et al, Meyer and Berens, Bowens et al, Steineck et al, and Srinivasan et al.
methadone dose.\textsuperscript{34} Thus, use of a formula-based approach could potentially overestimate the child’s needs, resulting in an increased risk of oversedation. Unlike other opioids, methadone has the potential to result in a prolonged rate-corrected QT (QTc) interval, as it is structurally similar to verapamil and has been associated with cardiac toxicity.\textsuperscript{22} One study retrospectively evaluated QTc prolongation in 36 children status-post cardiovascular surgery or with congenital heart disease that received methadone with a baseline and follow-up electrocardiogram.\textsuperscript{39} The investigators noted an increase in the QTc interval from baseline, 454 ± 41 msec versus 474 ± 51 msec, \( p = 0.034 \); further, they noted an increase in the number of children who met the criteria for QTc prolongation from baseline, 13 (36\%) versus 21 (58.3\%), \( p = 0.057 \), but this was not statistically significant. It is difficult to draw significant conclusions on the impact of enteral methadone on enteral methadone since these patients had a history of congenital heart disease. However, it is plausible that children receiving formula-based methadone dosing, whose dose would be higher than that of children receiving weight-based dosing, may be at greater risk of QTc prolongation as well. However, no evidence is available to suggest that children would be at higher risk than adults.

Using long-acting opioids for IOAS is similar to treating pain, in that each patient should be treated individually no matter the protocol used. Some emerging data suggest that genetic variance in opioid receptors would play a role in a child’s response to opioids.\textsuperscript{10,22} In light of the potential adverse events and concerns for genetic variation in opioid receptors, most high-risk patients’ IOAS symptoms could likely be managed with an initial, weight-based dose of methadone 0.1 mg/kg every 6 hours. Children with higher cumulative continuous infusion doses (eg, >2.5 mg/kg fentanyl), prolonged opioid exposure (eg, >14 days), and/or an active source of pain may require higher initial doses of methadone—0.2 to 0.4 mg/kg every 6 hours.\textsuperscript{22} In general, the patient’s long-acting opioid dose should be decreased by 10\% to 20\% every 24 to 48 hours.\textsuperscript{2,3,14} The available dosage form (eg, tablet vs oral liquid or concentration of the oral liquid) is one of the most important determinants of how the long-acting opioid can be tapered. The optimal taper duration also depends on the clinical status of the patient. Generally, the taper duration should not be longer than the duration of the opioid infusion. Clinicians should consider using standardized dosing guidelines to help limit the cumulative exposure of opioids beyond what the patient may require. One approach could entail use of a clinical pharmacist to aid in development of tapers; Steineck et al\textsuperscript{36} evaluated the use of a pharmacist-managed taper versus historical controls and found that the intervention decreased opioid exposure by 9 days.

Other agents could be considered for high-risk patients. Either enteral diazepam or lorazepam could be used to minimize the CNS and sympathetic symptoms in children with IOAS. In addition, children with prolonged exposure to a lorazepam or midazolam infusion may require a benzodiazepine taper. A discussion of benzodiazepine tapers is beyond the scope of this chapter due to the sake of depth and length. Other adjunct agents may include gabapentin, ketamine, and clonidine. A report in adults undergoing treatment for opioid detoxification suggested that gabapentin provided some relief in lower back pain and limb thrashing.\textsuperscript{40} In addition, Sacha and colleagues\textsuperscript{41} recently conducted a retrospective study in 22 neonates with refractory pain and agitation and found that gabapentin was able to reduce neonatal pain, agitation, and sedation (N-PASS) scores and lead to a reduction in the use of other sedatives or analgesics. Although the investigators did not explicitly evaluate gabapentin’s use for neonates with IOAS, it is feasible that this agent could be an option for children with CNS irritability and agitation. Another case report describes the use of a low-dose ketamine infusion at 1 mg/kg/h to alleviate IOAS symptoms in a 2 year-old with prolonged opioid exposure.\textsuperscript{42} Three small retrospective reports, representing a combined total of 22 patients, have described the use of transdermal or enteral clonidine either as
monotherapy or as an adjunct agent to prevent IOAS. Based on the limited evidence for these therapies, they should be considered as adjunct agents at this time.

**Prevention and Treatment of Dexmedetomidine Withdrawal**

Dexmedetomidine is a central α₂-agonist that stimulates the α₂-receptor on the presynaptic neurons in the locus coeruleus and inhibits the release of excitatory neurotransmitters. It is an attractive option over other sedatives due to its limited effects on respiratory mechanics, potential opioid-sparing effects, and potentially lower prevalence of the development of ICU delirium compared with benzodiazepines. Dexmedetomidine is FDA-labeled for sedation for less than 24 hours in mechanically ventilated adults; however, it is frequently used off-label in children. In fact, the RESTORE trial investigators noted that 36.1% of children enrolled in the usual care and intervention arms received dexmedetomidine.

Despite the routine use of dexmedetomidine in the PICU setting, limited studies have characterized the incidence of dexmedetomidine withdrawal. The incidence has ranged from 11.1% to 30% of children receiving prolonged infusions. The mechanism of dexmedetomidine withdrawal involves elevated concentrations of excitatory neurotransmitters available to agonize α₂-receptors on postsynaptic neurons. The most common withdrawal symptoms include CNS (ie, irritability, agitation, speech abnormalities, seizures) and sympathetic symptoms (ie, transient tachycardia and rebound hypertension). Other, more rare withdrawal symptoms have been reported, including adrenal suppression following abrupt cessation of dexmedetomidine. Some reports have described the development of GI dysfunction (ie, diarrhea, emesis) that was potentially attributed to dexmedetomidine. Children in these reports were also receiving an opioid infusion or epidural with opioids. As central α₂-agonists have no activity in the GI tract, it seems likely that the GI dysfunction would have been attributed to the opioids rather than dexmedetomidine.

Limited studies have characterized risk factors for dexmedetomidine withdrawal. Honey and colleagues found that children with a cumulative dexmedetomidine infusion dose of 8.5 μg/kg or more were at greater risk for adverse events and withdrawal symptoms. However, some have proposed that children receiving 4 to 5 days of dexmedetomidine infusions may also be at risk of withdrawal following abrupt discontinuation. Since the half-life of dexmedetomidine is approximately 2.65 hours in children, they would achieve a steady-state concentration within approximately 13 hours following initiation of dexmedetomidine. Therefore, it is plausible that children could experience withdrawal symptoms following abrupt discontinuation even with shorter courses of dexmedetomidine (ie, 48-72 hours).

Two strategies could be used to prevent or treat dexmedetomidine withdrawal. Table 3 provides recommendations for children with low risk and high risk of dexmedetomidine withdrawal. Given its relatively short half-life, dexmedetomidine could be tapered by 0.1 μg/kg/h every 8 to 12 hours. However, this may not be the most practical approach for children with cumulative doses of 8.5 μg/kg or more and/or infusion durations of 5 days or longer, since it could prolong PICU length of stay and theoretically could increase the risk of central line-associated bloodstream infections.

Table 3 provides recommendations for children at high risk of dexmedetomidine withdrawal. Clonidine is available in the United States as an enteral tablet, a compounded oral solution, and a transdermal patch. To date, 1 abstract and 3 small studies have evaluated use of clonidine to prevent dexmedetomidine withdrawal. Clonidine can be administered as an enteral or epidural infusion. Three of these reports evaluated enteral clonidine in adults. Glisic and colleagues retrospectively evaluated 19 adults who were transitioned to enteral clonidine (daily dose 0.2-1.2 mg). The
Terry et al. retrospectively evaluated 26 adults receiving enteral clonidine. Although the mean dose was not provided, the investigators noted that the majority received 0.1 mg every 6 to 8 hours. They noted that 17 patients (65.4%) were able to transition off dexmedetomidine within 8 hours following clonidine initiation. However, one potential negative finding was that a number of patients were not tapered off of clonidine, with 54% and 23% of patients still receiving clonidine upon transition to the floor and at discharge, respectively. Gagnon and colleagues performed a prospective, pilot study in 20 adults receiving dexmedetomidine who were transitioned to 0.3 mg of enteral clonidine every 6 hours. This dose was notably higher than those in the other 2 reports. The investigators noted that 15 patients (75%) were able to transition off dexmedetomidine within 48 hours of clonidine initiation. Based on these findings, enteral clonidine appears to be a plausible option in adults to prevent dexmedetomidine withdrawal.

Only 1 report has evaluated the use of clonidine to prevent dexmedetomidine withdrawal in children. Lardieri and colleagues performed a retrospective study evaluating the use of transdermal clonidine in 12 out of 20 treatment courses of dexmedetomidine at “high risk” of withdrawal. There was a significant difference in the cumulative dexmedetomidine exposure in children receiving clonidine (n = 12) versus no clonidine (n = 8), 232.7 mcg (IQR 158.3-336.1) versus 126.1 mcg (IQR 102.1-157.5), p = 0.031. In the 12 children receiving clonidine, they received either a 0.05-mg (n = 1) or 0.1-mg (n = 11) clonidine patch. The investigators compared Withdrawal Assessment Tool-1 (WAT-1) scores and found comparable scores in those patients receiving clonidine versus those who did not. However, the investigators also noted that fewer children receiving clonidine had elevated WAT-1 scores in the first 24 hours following dexmedetomidine discontinuation. Although these data were collected retrospectively and involved a small sample size, the report provides some supporting data for children at risk of dexmedetomidine withdrawal.

Based on these studies, it appears that clonidine may be a viable option for dexmedetomidine withdrawal. However, some practical issues should be considered regarding transdermal patches and enteral clonidine. In a recent systematic review, Capino and colleagues evaluated the use of clonidine for sedation and analgesia for drug withdrawal; they noted that the dosing for children initiated on transdermal clonidine for clinical outcomes of drug withdrawal ranged from 2.9 to 18.2 μg/kg/d. The

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Therapeutic Approaches</th>
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<tr>
<td>Low risk*</td>
<td>Taper dexmedetomidine infusion by 0.1 μg/kg/h every 8-12 hours until discontinued.</td>
</tr>
<tr>
<td>High risk*</td>
<td>Transdermal clonidine: 5-8 μg/kg/d administered using the nearest commercially available clonidine patch (0.1, 0.2, 0.3 mg/d); do not use in children &lt;1 year; do not cut or occlude patch with transparent film. Enteral clonidine: 5-8 μg/kg/d divided every 8 hours PO using commercially available clonidine tablets (0.1, 0.2, 0.3 mg) or an extemporaneously compounded oral solution (0.01, 0.02, or 0.1 mg/mL)</td>
</tr>
</tbody>
</table>

*Low-risk patients include children with <8.5 μg/kg or <5 days of dexmedetomidine infusion exposure.

*High-risk patients include children with ≥8.5 μg/kg or ≥5 days of dexmedetomidine infusion exposure.

Data from Johnson, Honey et al, Honey et al, and Capino et al.
dosing range for this formulation is likely wide in these reports due to the fixed dosage forms of transdermal patches available as 0.1-, 0.2-, and 0.3-mg/d patches. Some authors have proposed either cutting the patches or using a transparent film dressing to occlude the patch into quarters (eg, 0.025 mg/d) or halves (eg, 0.05 mg/d) to provide a specific dose; however, this practice should be avoided due to pharmacokinetic and logistical concerns. Zuppa et al\textsuperscript{57} evaluated the clonidine pharmacokinetics in 15 children receiving whole and cut patches; the investigators noted that children who had whole patches had more predictable concentrations and children who received cut patches had significantly higher clonidine concentrations. Additionally, to the author’s knowledge, no studies have evaluated the pharmacokinetics of clonidine when portions of the patch are occluded with a transparent film dressing. Furthermore, clonidine patches are very small, and it is logistically difficult to accurately cut or cover a desired portion of the patch. As well, such modifications could prevent the remaining portion of the patch from adhering to the patient’s skin. Next, it is the author’s opinion that clonidine patches should be avoided in children younger than 1 year due to the potential for increased absorption from transdermal patches, given these patients’ thinner stratum corneum and larger surface-to-volume ratio than older children. The onset and duration of transdermal clonidine should be considered. Transdermal clonidine has a slower onset than enteral clonidine, 2 to 3 days versus 30 to 60 minutes, respectively.\textsuperscript{21} This delay in onset could significantly affect the clinician’s ability to quickly discontinue the child’s dexmedetomidine infusion. The labeling for clonidine patches suggests that the duration of wear is 7 days. However, many sources suggest that the duration of effect in children is much shorter, requiring the patches to be changed every 3 to 5 days.\textsuperscript{21} Leaving the patches in place for 7 days could diminish the efficacy of clonidine to prevent dexmedetomidine withdrawal the last 2 to 4 days of the dosage interval in children.\textsuperscript{21}

Although no studies in children have evaluated enteral clonidine for prevention of dexmedetomidine withdrawal, several reports have evaluated the use of enteral clonidine to prevent other types of drug withdrawal in the PICU for infants and children. Capino and colleagues\textsuperscript{21} noted in their systematic review that the initial dose for this indication ranged from 2 to 8 μg/kg/d divided every 6 to 8 hours.\textsuperscript{21} In addition, a clonidine dosage regimen of 5 to 12 μg/kg/d divided every 3 to 6 hours has been used for neonates with NAS.\textsuperscript{58} Based on a study by Arenas-Lopez and colleagues\textsuperscript{59} evaluating clonidine pharmacokinetics in critically ill children, steady-state concentrations should be achieved in approximately 41 hours. Therefore, an every 8-hour dosing interval seems appropriate, and the more frequent dosing of every 3 to 6 hours in neonates with NAS would be unnecessary. However, clinicians should note that some critically ill patients with altered cardiac output may have diminished enteral absorption. Arenas-Lopez and colleagues\textsuperscript{60} evaluated the pharmacokinetics of enteral clonidine in infants and children with congenital heart surgery following cardiac surgery and noted significant variation in the time needed to attain therapeutic concentrations. These findings indicate that pediatric patients who have undergone cardiac surgery or those requiring hemodynamic support may have diminished absorption and delayed onset time of enteral clonidine. As a result, these children may need increased doses of clonidine to achieve a therapeutic effect. For children who are initiated on enteral clonidine, both commercially available tablets and extemporaneously compounded oral solutions could be used. A variety of compounded recipes for enteral clonidine exist, including 0.01, 0.02, and 0.1 mg/mL, and this could create some significant safety concerns for transitions of care (eg, hospital discharge or transfer to other facilities).\textsuperscript{21}

Until further studies are conducted, transdermal patches or enteral clonidine could be used to prevent dexmedetomidine withdrawal with an initial starting dose of 5 to 8 μg/kg/d administered as a patch or in divided doses.
administered every 8 hours when given enterally. The transdermal patch should not be used in children younger than 1 year due to concerns of altered dermal absorption. If the transdermal patch is used, clonidine patches should not be cut or occluded with a transparent film dressing. Future prospective studies should be conducted to further elucidate clonidine’s role for treatment of dexmedetomidine withdrawal using a validated tool to assess drug withdrawal.

**Assessment Considerations**

When managing drug withdrawal in the PICU, clinicians must use a validated tool to assess drug withdrawal. A variety of assessment tools have been developed to assess drug withdrawal in neonates and children. Table 4 provides a brief description of 3 of the most common tools that have been used to assess signs of drug withdrawal in infants and children.

**Table 4. Comparison of Selected Drug Withdrawal and ICU Delirium Scales in Children**

<table>
<thead>
<tr>
<th>Drug Withdrawal Scales</th>
<th>Delirium Scales</th>
</tr>
</thead>
<tbody>
<tr>
<td>Validated in PICU setting</td>
<td>No</td>
</tr>
<tr>
<td>No. of items</td>
<td>21</td>
</tr>
<tr>
<td>Parameter assessed</td>
<td>Neonatal abstinence syndrome</td>
</tr>
<tr>
<td>Basis of assessment</td>
<td>Clinician observation</td>
</tr>
<tr>
<td>Range of points</td>
<td>0-45</td>
</tr>
</tbody>
</table>

**Specific assessment components:**

**Central nervous system**

- Motor (uncoordinated/repetitive movements, tremor, myoclonus, startle, grimace): X, X, X, X
- Behavior (agitation, irritability, abnormal cry, sucking, excoriation): X, X, X, X
- State (sleep, time to calm, inconsolability, restlessness, altered mental status): X, X, X, X, X

**Psychiatric (hallucinations, anxiety, delusions, psychomotor retardation)**: X, X

**Interaction (eye contact, response time, organized thinking, attention)**: X, X, X

**Seizures**: X

**Sneezing**: X, X, X

**Yawning**: X, X
Clinicians should be mindful of a number of different considerations regarding assessment tools for drug withdrawal. First, these tools are limited in differentiating withdrawal symptoms between sedative and opioid agents. The modified Finnegan Scoring System was designed to assess withdrawal symptoms in neonates with NAS following in utero opioid exposure. In contrast, the Sophia Observational Withdrawal Symptom Scale (SOS-PD) and the WAT-1 have been validated in the PICU setting to assess both opioid and benzodiazepine withdrawal. Currently, no tools have been validated to assess dexmedetomidine withdrawal. In a small study, Lardieri and colleagues used the WAT-1 to assess dexmedetomidine withdrawal, but it is difficult to draw significant conclusions based on the small sample size. As noted, symptoms of dexmedetomidine withdrawal include irritability, agitation, seizures, rebound hypertension, and transient tachycardia. Many of these symptoms would be captured based on the assessment criteria as noted in Table 4. However, none of the tools depicted in Table 4 assess blood pressure, so clinicians should monitor changes in blood pressure in conjunction with routine assessment using one of these validated tools. For children exposed to multiple sedative and opioid agents, it may be difficult to differentiate between withdrawal symptoms to determine the medication causing withdrawal. Opioids, benzodiazepines, and dexmedetomidine withdrawal symptoms are associated with CNS irritability and autonomic dysfunction, but dexmedetomidine and benzodiazepines do not have activity in the GI tract and thus are not classically associated with GI dysfunction withdrawal symptoms. Therefore, withdrawal symptoms that are primarily associated with GI dysfunction would most likely be due to IOAS. Opioid withdrawal and dexmedetomidine withdrawal are both associated with hypertension, so the timing of these withdrawal symptoms in relation to when the infusions are discontinued may aid in differentiating the origin of the withdrawal. With dexmedetomidine’s relatively short half-life of 2.65 hours, it is more likely that the onset of rebound hypertension would occur in the first 12 to 48 hours following dexmedetomidine discontinuation. In contrast, opioid infusions have much longer half-lives when administered as a continuous infusion, so onset of hypertension would likely be more prolonged. For example, the context-sensitive half-life of

### Table 4. Comparison of Selected Drug Withdrawal and ICU Delirium Scales in Childrena (continued)

<table>
<thead>
<tr>
<th>Drug Withdrawal Scales</th>
<th>Delirium Scales</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specific assessment components:</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal system:</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>X</td>
</tr>
<tr>
<td>Loose stools</td>
<td>X</td>
</tr>
<tr>
<td>Sympathetic system:</td>
<td></td>
</tr>
<tr>
<td>Palpitations/tachycardia</td>
<td>X</td>
</tr>
<tr>
<td>Sweating</td>
<td>X</td>
</tr>
<tr>
<td>Tachypnea</td>
<td>X</td>
</tr>
<tr>
<td>Temperature elevation</td>
<td>X</td>
</tr>
</tbody>
</table>

aData from Franck et al, Ista et al, Smith et al, and Traube et al.
fentanyl infusions in children is approximately 21 hours. As a result, children may experience withdrawal symptoms including hypertension for up to 5 days after their fentanyl infusion is discontinued.

Assessment of iatrogenic drug withdrawal in neonates and infants entails some specific considerations. Although the modified Finnegan tool has not been validated in the PICU setting, it is the most predominant scoring tool used in US neonatal ICUs, and the 2012 guidelines from the American Academy of Pediatrics mention that this tool could be used to assess drug withdrawal symptoms for neonates and infants with iatrogenic drug withdrawal. Recent studies have raised some significant concerns about the application of the modified Finnegan tool to assess symptoms in infants. Zimmerman-Baer and colleagues performed an observational cohort study that assessed the variability of modified Finnegan scores during the first week of life (cohort 1) compared with weeks 5 or 6 of life (cohort 2) in infants who were not exposed to opioids. The investigators found variability in the upper end of scores: 5.5 versus 7. In addition, they noted diurnal variation in the median scores during the day and night: 5 versus 2. The investigators concluded that the older infants or infants assessed during day-time may have higher scores based on receiving points for criteria that may be normal for infants rather than representative of withdrawal. Based on these findings, it appears that the modified Finnegan tool has limited utility in infants with iatrogenic drug exposure in the PICU setting.

One last consideration is the likely overlap between the manifestations of drug withdrawal and PICU delirium. In adult ICUs, delirium is estimated to occur in 60% to 80% of mechanically ventilated adults and is associated with an increased ICU length of stay, hospital cost, and mortality. Until recently, limited epidemiological studies have evaluated pediatric delirium in the PICU setting due to a lack of validated assessment tools. Table 4 provides an overview of 3 validated assessment tools developed in the last 5 to 10 years to assess for pediatric delirium, including the Cornell Assessment of Pediatric Delirium (CAPD), the Pediatric Confusion Assessment Method (pCAM-ICU), and the Preschool Confusion Assessment Method (psCAM-ICU). When the specific components of these 3 pediatric delirium tools are compared with the modified Finnegan, SOS-PD, and the WAT-1, an overlap is noted in the motor, behavior, and state CNS criteria (Table 4). In addition, the SOS-PD and the CAPD were validated to assess psychiatric symptoms including hallucinations and delusions.

The overlap in the manifestations between drug withdrawal and delirium may make it difficult for clinicians to differentiate whether a patient’s symptoms are due to drug withdrawal or delirium, resulting in misdiagnosis and mismanagement. Both of these complications occur frequently in the PICU. As noted, iatrogenic drug withdrawal has been noted in 11.1% to 68% of children. Recently, Traube et al conducted a multicenter delirium point-prevalence study and reported that 25% of children were noted to have delirium. The investigators also noted that age younger than 2 years, use of physical restraints, and exposure to benzodiazepines, opioids, and antiepileptics were independently associated with delirium. The difficulty in differentiating between delirium and iatrogenic drug withdrawal has significant implications given that the management protocols for delirium and drug withdrawal are very different. Future research should be focused on the development of new delirium and withdrawal assessment tools that attempt to address this overlap. In addition, Madden and colleagues suggest that future research focus on the adjustment of the current delirium and drug withdrawal tools by using differential weighting of the signs and symptoms of delirium and iatrogenic drug withdrawal. Until this future research can be conducted, clinicians should be mindful of the potential overlap between delirium and drug withdrawal assessment tools and should consider patient-specific factors such as medication history (ie, benzodiazepines, antiepileptics) and history of physical restraints.
that may help differentiate between these 2 complications to determine the most appropriate interventions to alleviate patients’ symptoms.

Summary
Iatrogenic drug withdrawal is a frequent complication in critically ill children that can occur following abrupt discontinuation of a prolonged course (>5 days) of opioid and sedative infusions. The need for prevention or treatment of opioid and dexmedetomidine withdrawal can often be determined based on the patient’s total duration of exposure and cumulative dose. For patients at risk of iatrogenic drug withdrawal, a validated tool should be used consistently to help guide management. Clinicians should be mindful, though, of overlap between delirium and withdrawal assessment tools and should use patient-specific factors to help determine the most appropriate interventions to manage their patients’ symptoms.

REFERENCES
15. Tobias JD. Dexmedetomidine to treat opioid withdrawal in infants following prolonged sedation in the pediatric ICU. J Opioid Manag. 2006;2:201-205.


