Opioids and benzodiazepines are mainstays of sedation and analgesia in the pediatric intensive care unit (PICU). Use of these medications often requires a balance of pain relief and sedation, along with the management of narcotic withdrawal. Narcotic withdrawal syndromes were first described in the neonatal population in the 1970s. Only in the last 20 years have narcotic withdrawal syndromes been recognized in other pediatric patients; most cases are a result of iatrogenic exposure to narcotics during long hospital stays. Dexmedetomidine is an $\alpha_2$-adrenergic receptor agonist that has the potential to decrease narcotic withdrawal symptoms. While published data are available regarding the use of dexmedetomidine as an adjunct for sedation and analgesia in pediatric patients, there are limited data on the use of dexmedetomidine for pediatric narcotic withdrawal syndromes. For this review, clinical studies were evaluated to assess the appropriateness of dexmedetomidine use in this population.

Withdrawal may be difficult to assess in the PICU due to the wide variability and nonspecificity of objective and subjective withdrawal symptoms. Several retrospective studies have reported withdrawal symptoms in 35–57% of children receiving continuous infusion opioids and benzodiazepines. The increased awareness of narcotic withdrawal in the pediatric population has led to questions as to how to best prevent and treat pediatric narcotic withdrawal.

Withdrawal symptoms are often related to sympathetic system acti-
The Clinical Consultation section features articles that provide brief advice on how to handle specific drug therapy problems. All articles are based on a systematic review of the literature. The assistance of ASHP’s Section of Clinical Specialists and Scientists in soliciting Clinical Consultation submissions is acknowledged. Unsolicited submissions are also welcome.

Opioid and benzodiazepine withdrawal

Benzodiazepines provide sedation via attachment to γ-aminobutyric receptors in the central nervous system (CNS). The result is a decrease in sympathetic outflow, which results in sedation. Withdrawal has been seen with a wide duration of use: from 11 hours to two months. A retrospective chart review involving 40 pediatric patients found a 35% rate of withdrawal in patients receiving midazolam continuous infusions. Other research indicates that patients who receive a cumulative midazolam dosage of 60 mg/kg or higher are more likely to experience withdrawal.

Fentanyl is a rapid-acting, synthetic mu-opioid receptor agonist. Fentanyl is a highly lipid-soluble drug and distributes effectively into adipose tissue. Acidosis can increase the capacity of fentanyl to bind to muscle and adipose tissue, resulting in prolongation of fentanyl storage. The delayed release of fentanyl from muscle and adipose tissue may result in delayed withdrawal.

The rate of withdrawal in pediatric patients receiving fentanyl continuous infusions has been reported as 57%. Katz et al. performed a retrospective study of 23 infants who received at least 24 hours of continuous infusion fentanyl. Withdrawal was seen in 13 of the 23 infants; those who experienced withdrawal had higher mean cumulative fentanyl dosages (2.96 mg/kg versus 0.53 mg/kg) and a longer mean duration of fentanyl use (13.1 days versus 3.8 days). Other studies have shown that a total fentanyl dosage of ≥1.5 mg/kg or a duration of use of 5 days or more resulted in a 50% rate of withdrawal. Patients receiving dosages of ≥2.5 mg/kg or infusions lasting 9 days or more had a 100% rate of withdrawal.

The choice of pharmacotherapy for prevention of narcotic withdrawal through use of tapering schedules varies among institutions. The most common agents used are morphine, methadone, diazepam, lorazepam, and phenobarbital. Regardless of the medication chosen, an important aspect is observation for signs, symptoms, and alleviation of withdrawal.

Withdrawal assessment scales

Assessment of pediatric narcotic withdrawal is not standardized, and a variety of approaches are in current use. Using a scoring system is an effective way to standardize the evaluation of narcotic withdrawal, and there are several scoring systems available; while all have limitations, they can help guide assessment for narcotic withdrawal. Of the six scales currently used for assessment of pediatric withdrawal, several were developed specifically for use in newborns and infants.

One widely used assessment tool is the Neonatal Abstinence Score developed by Finnegan et al. for evaluation of newborns and infants for withdrawal resulting from maternal exposure to narcotics. Using this method, also known as the Finnegan Scoring System (FSS), patients are assessed for the presence and severity of 31 signs and symptoms in three categories (CNS, gastrointestinal, and metabolic/vasomotor/respiratory); each sign or symptom is assigned a score of 1–5, with an aggregate score of 0–7 indicating mild withdrawal, a score of 8–11 indicating moderate withdrawal, and a score of 12–15 indicating severe withdrawal. As several of the signs and symptoms are specific to neonates and infants, the use and clinical utility of the Finnegan method in older pediatric patients are limited; the method also is thought by some to be too complicated for use in the PICU setting. Nonetheless, the method can be useful in the clinical assessment of opioid and benzodiazepine withdrawal in children.

Other clinical assessment tools specifically designed for assessment of withdrawal in children receiving long-term opioid therapy in the PICU include the Sedation Withdrawal Scale (SWS), derived from assessment of 12 neonatal signs and symptoms, and the Opioid–Benzodiazepine Withdrawal Scale (OBWS), which is used to evaluate 16 parameters adapted from the Finnegan method. The validity and reliability of the SWS...
and OBWS have not been firmly established.

**Use of dexmedetomidine**

Current pharmacotherapy regimens for narcotic withdrawal consist of other narcotic agents. Clonidine has been shown to have a role in neonatal abstinence syndrome (NAS) and is used as an adjunctive therapy for opioid withdrawal in adults. Agathe et al. found that the use of oral clonidine hydrochloride 1 µg/kg/dose every four hours as an adjunct to diluted tincture of opium resulted in a 27% decrease in the median length of therapy for NAS.

Dexmedetomidine’s chemical structure is similar to that of clonidine, but the former has a greater specificity for the α2- (as opposed to α1) receptor (1620:1 for dexmedetomidine versus 220:1 for clonidine). With both drugs, activation of α2-receptors results in analgesia, sedation, and anxiolysis. Due to the drugs’ similar mechanisms of action, it has been hypothesized that dexmedetomidine, like clonidine, may have a role in the management of opioid withdrawal syndromes.

When used as an adjunct for sedation and analgesia, dexmedetomidine was administered at a continuous infusion range of 0.1–1.4 µg/kg/hr. Several studies have indicated a median effective dose of 0.6–1 µg/kg/hr. Carroll et al. reported a median effective dose of 0.7 µg/kg/hr in patients who received dexmedetomidine for more than 24 hours (either as an adjunct, in anticipation of extubation, or alone for sedation) and a median effective dose of 0.9 µg/kg/hr when dexmedetomidine was used as an adjunct for sedation. Patients who received dexmedetomidine for more than 24 hours required higher median doses (0.5 µg/kg/hr versus 1 µg/kg/hr), indicating that there may be some tachyphylaxis with extended use. The variability in the dosage range of dexmedetomidine observed in the study may be a reflection of the small sample size of patients and substantial variability of individual patient response, emphasizing the need for clinical trials to determine effective dosing.

**Literature review.** A PubMed search using the terms pediatric narcotic withdrawal, dexmedetomidine, Precedex, clonidine, and pediatric sedation was performed to identify articles addressing use of dexmedetomidine hydrochloride for narcotic withdrawal in pediatric patients. The published literature on dexmedetomidine use for opioid withdrawal mainly consists of several case studies and two retrospective reviews involving a total of 20 pediatric patients.

Bejian and colleagues found a decrease in total daily doses of fentanyl (mean ± S.D., 16.58 ± 4.2 µg/kg/day versus 47.5 ± 15.1 µg/kg/day) and midazolam (0.26 ± 0.1 mg/kg/day versus 1.08 ± 0.47 mg/kg/day) in 45 pediatric patients who received dexmedetomidine when compared with those who did not receive the drug. The decreased opioid requirements reported with dexmedetomidine use might help reduce the rate of withdrawal and allow shorter tapering schedules.

Finkel et al. discussed two pediatric patients who received dexmedetomidine for prevention of withdrawal and to aid in acute discontinuation of fentanyl and midazolam continuous infusions at a bolus dose of 1 µg/kg over 10 minutes and a continuous infusion rate of 0.2–0.7 µg/kg/hr. Bolus doses were given every six hours until the cumulative dose was 0.7 µg/kg/hr and the BIS was over 80, or until arterial blood pressures were greater than 20% of baseline. Bolus doses were needed on days 2–4. Dexmedetomidine was tapered on day 7, and no symptoms of narcotic withdrawal were seen in the following two weeks.

Baddigam et al. reported on three pediatric patient cases in which dexmedetomidine was used for treatment of withdrawal syndromes. In one case, dexmedetomidine was started due to a diagnosis of drug and substance withdrawal. In the other two cases, dexmedetomidine was used when withdrawal symptoms were observed three to five days after surgery while the patients were receiving continuous infusion fentanyl (4–6 µg/kg/hr) and intermittent midazolam (0.1 mg/kg/dose every two hours as needed); one of those patients required four midazolam doses per day, and the other required four to eight doses per day. Dexmedetomidine was started after withdrawal symptoms were seen us-
ing a bolus dose of 0.5 μg/kg over 15 minutes, followed by a continuous infusion at 0.25 μg/kg/hr, with a maximum infusion rate of 0.6 μg/kg/hr. All three patients experienced amelioration of their withdrawal symptoms (hypertension, tachycardia, diaphoresis, agitation, and tremors) with dexmedetomidine.

Two retrospective studies assessed the use of dexmedetomidine for opioid withdrawal in pediatric patients.23,24 The first study reported on seven infants (3–24 months old) who had received continuous fentanyl infusions with intermittent midazolam for extubation procedures.24 Fentanyl and midazolam exposure was four to nine days, with a fentanyl infusion range of 4–9 μg/kg/hr. All seven patients had Finnegan scores of 12 or more along with signs and symptoms of severe withdrawal. Dexmedetomidine was given for treatment of withdrawal as a bolus of 0.5 μg/kg over 10 minutes, followed by a continuous infusion at 0.5 μg/kg/hr. After the addition of dexmedetomidine, Finnegan scores were consistently 7 or lower. The dexmedetomidine dose was decreased by 0.1 μg/kg/hr every 12–24 hours.24 The second study assessed use of a subcutaneous continuous infusion of dexmedetomidine for prevention or treatment of withdrawal in seven pediatric patients (the patients required i.v. access solely for the purpose of the dexmedetomidine continuous infusion).23 The subcutaneous continuous infusion was initiated at the same rate as the i.v. infusion (0.8–1.4 μg/kg/hr). Subcutaneous dexmedetomidine was used for periods of four to seven days, with no reported adverse effects and modified Finnegan scores ranging from 3 to 7, suggesting that subcutaneous continuous infusion may be an alternative to i.v. continuous infusion for delivery of dexmedetomidine.23

**Limitations of published evidence.** The available literature on dexmedetomidine use for prevention or treatment of narcotic withdrawal is limited. While the studies and case reports described here provide useful insights, they involved a total of only 20 patients, and 90% of the patients were less than four years old. In addition, all five case reports (most by the same author) described the use of bolus doses; although it is not reported in the literature, many institutions do not use bolus doses of dexmedetomidine due to the risk of adverse events. Moreover, the range of reported continuous infusion rates is wide, and rates were typically titrated to patient response, with the dose-limiting factors being hypotension and bradycardia. In addition to those issues, the package insert states that dexmedetomidine is to be used for less than 24 hr.26 In all of the reports described here, dexmedetomidine was used for 2–16 days without additional adverse events or development of withdrawal symptoms.

**Adverse events.** Dexmedetomidine is an imidazole compound specific for the α₂-adrenergic receptors in the brain and spinal cord. Its inhibition of neuronal firing in the CNS also results in hypotenion and bradycardia, which are dose-dependent, common adverse effects of dexmedetomidine.22 Dexmedetomidine does not have direct effects on the hemodynamics of the heart. Bolus doses of dexmedetomidine have been found to be commonly associated with hypotension and bradycardia, which are thought to be mediated by the effects of dexmedetomidine on α₂-adrenergic receptors in the brain and spinal cord at high doses. In addition, it has been hypothesized that rapid boluses may produce some peripheral α₁B-receptor stimulation; that is overcome with slow infusion.

Few studies have been conducted to assess adverse events associated with use of dexmedetomidine in pediatric patients. In adults, the most common adverse events are hypotension (30% of reported cases), hypertension (12% of cases), and bradycardia (9% of cases).27 Honey et al.28 conducted a retrospective study of 36 pediatric patients (median age, 3.2 years; range, 0.01–16.75 years) who received dexmedetomidine for at least two hours during a total of 41 infusions. They found an overall adverse event rate of 51%; bradycardia and hypotension occurred in 15% and 22% of cases, respectively. The frequency of hypotension and bradycardia reported by Honey et al.28 is higher than that reported in other retrospective studies.19 In the review conducted by Carroll et al.,18 bradycardia was seen in 3% of cases and hypotension in 9% of cases, which is consistent with the findings of other studies. The patients in the study by Carroll et al. ranged from 0.1 to 17.2 years of age, with a median age of 1.5 years. Hypotension and bradycardia are thought to be associated more with use of bolus doses than with continuous infusion of dexmedetomidine; that might explain the discrepant adverse-event rates reported in the study by Carroll et al.,18 which did not include patients who received bolus doses of dexmedetomidine, and the study by Honey et al.,28 in which 43.9% of patients received bolus doses.

There is a potential for withdrawal after the discontinuation of long-term infusions of dexmedetomidine. Defining long-term dexmedetomidine use is difficult. As previously mentioned, dexmedetomidine has a mechanism of action similar to that of clonidine, and withdrawal symptoms have been reported after rapid discontinuation of long-term clonidine therapy administered by oral, epidural, and transdermal routes.29 While more data on withdrawal after rapid discontinuation of dexmedetomidine are needed, a few case reports indicate that tolerance and withdrawal phenomena can occur.7,30,31 Proposed mechanisms for development of tolerance include receptor

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**Clinical Consultation**

**Dexmedetomidine**
desensitization via loss of receptors or receptor–effector uncoupling.

Relief of withdrawal symptoms such as hypertension, tachycardia, emesis, agitation, facial drooping, decreased verbal communication, and tonic–clonic seizures has been reported with reinitiation of dexmedetomidine. Unlike the reported experience with other continuous infusion medications for sedation and analgesia, the symptoms of dexmedetomidine withdrawal (e.g., agitation, irritability, dystonic movements, centrally mediated rebound hypertension) appear to be CNS related, with no hemodynamic manifestations.

Discussion

Dexmedetomidine is an α2-agonist whose use in the PICU has increased in the last few years as an adjunct to sedation and analgesia. The use and typical dosages of dexmedetomidine vary, primarily due to concern about potential hypotension and bradycardia, which have been reported in the published literature in association with the use of bolus doses. When bolus doses are used, a typical loading dose is 0.5–1 μg/kg given intravenously over 10 minutes; bolus doses are followed by a continuous infusion of 0.1–1.4 μg/kg/hr.

Dexmedetomidine has the benefits of being an effective adjunct therapy for sedation and analgesia without producing the respiratory depression seen with most other sedatives and analgesics. In addition, when used as an adjunct, dexmedetomidine allows for decreased fentanyl and midazolam requirements. Common adverse effects of dexmedetomidine use are hypotension and bradycardia; these effects are thought to be related to the use of bolus doses, high cumulative doses, and longer duration of therapy. The majority of published reports about the use of dexmedetomidine in pediatric patients only describe its use for analgesia and sedation.

Dexmedetomidine has a mechanism of action similar to that of clonidine, with the benefit of greater selectivity for the α2-receptor. Dexmedetomidine may have a role in decreasing the occurrence of narcotic withdrawal after discontinuation of continuous infusion opioids and benzodiazepines in pediatric patients. While the available evidence demonstrates the usefulness of dexmedetomidine in pediatric critical care, questions persist as to the drug’s safety and efficacy for analgesia and sedation. Data on use of dexmedetomidine specifically for the prevention and treatment of opioid and benzodiazepine withdrawal are limited, indicating the need for additional well-designed studies exploring its use for pediatric narcotic withdrawal.

Conclusion

A limited body of published evidence from retrospective studies and case reports suggests a potential role for dexmedetomidine as an adjunct therapy to provide sedation and analgesia to reduce narcotic withdrawal symptoms in pediatric patients.

References

23. Tobias JD. Subcutaneous dexmedetomidine infusions to treat or prevent drug


