Efficacy of $\alpha_2$-Agonists for Sedation in Pediatric Critical Care: A Systematic Review*

John C. Hayden, MPharm1; Cormac Breathnach, MB, BCh, BAO, FJFICM2; Dermot R. Doherty, MD, FCARCSI, FJFICMI2,3; Martina Healy, MB, BCh, BAO, FFARCSI, FJFICM2; Moninne M. Howlett, BSc1,2; Paul J. Gallagher, PhD1; Gráinne Cousins, PhD1

Objective: Children in PICUs normally require analgesics and sedatives to maintain comfort, safety, and cooperation with interventions. $\alpha_2$-agonists (clonidine and dexmedetomidine) have been described as adjunctive (or alternative) sedative agents alongside opioids and benzodiazepines. This systematic review aimed to determine whether $\alpha_2$-agonists were effective in maintaining patients at a target sedation score over time compared with a comparator group. We also aimed to determine whether concurrent use of $\alpha_2$-agonists provided opioid-sparing effects.

Data Sources: A systematic search was performed using the Cochrane Central Register of Controlled Trials, PubMed, EMBASE, CINAHL, and LILACS.

Study Selection: We included randomized controlled trials of children in PICU treated with clonidine or dexmedetomidine for the indication of sedation.

Data Extraction: Two authors independently screened articles for inclusion.

Data Synthesis: Six randomized controlled trials with sufficient data were identified and critically appraised. Three clonidine trials (two vs placebo and one vs midazolam) and three dexmedetomidine trials (two vs fentanyl, one vs midazolam) were included. Due to study heterogeneity it was not possible to pool studies. A narrative synthesis is provided.

Conclusions: Reporting of study results using the outcome "time maintained at target sedation score" for clonidine or dexmedetomidine was poor. Only one trial compared clonidine with midazolam using a sedation score outcome. This study was underpowered to demonstrate equivalence to midazolam as a sedative. The adjunctive use of clonidine demonstrated significant decreases in opioid use in neonates but not in older groups. Clonidine dose was inconsistent between studies. Dexmedetomidine demonstrated an opioid-sparing effect in two small trials. Further studies, including dose-finding studies and studies with sedation score–based outcomes, are needed. (Pediatr Crit Care Med 2016; 17:e66–e75)

Key Words: adrenergic $\alpha_2$-receptor agonists; children; clonidine; critical care; dexmedetomidine; sedation

Most critically ill children in PICUs require sedative and analgesic medications to provide a continuous level of comfort or to facilitate stressful interventions, such as mechanical ventilation. Sedatives are also administered to attenuate the stress response and reduce metabolic demands during periods of cardiac, respiratory, and neurologic instability (1, 2).

Current practice in sedation in PICUs varies widely because of the paucity of well-conducted randomized controlled trials (RCTs) to assess safety and efficacy of medicines used in this group. The goal of therapy is to have most patients free of distress and somewhat interactive with their environment (3).

Consensus statements on analgesia and sedation in critically ill children recommend continuous infusion of morphine or fentanyl for relief of severe pain (4). Combination therapy of sedatives and analgesics is often required to optimize sedation in critically ill children. A survey in the United Kingdom described...
24 agents being used across 360 patients. Morphine (78%) and midazolam (55%) were the most common agents used (5).

Continuous infusion morphine, an analgesic at lower doses and sedative at higher, is the preferred opioid analgesic because of its marked sedative properties in PICUs (6). Yet, opioids are well known to produce tolerance, dependence, and a number of unwanted side effects. Midazolam has also been established as an effective sedative agent in the PICU environment (7). However, it shares the potential side effects of tolerance, dependence, withdrawal, and respiratory depression with morphine, in addition to potential cardiovascular depression. Animal models have also suggested potential for impaired neurodevelopment (7, 8).

The α₂-agonists clonidine and dexmedetomidine represent a potential nonbenzodiazepine alternative for PICU sedation (4). Their alternative mechanism of action has been reported to achieve desirable sedation in adults without some of the less desirable side effects associated with the established agents (9). α₂-agonists have a sympatholytic effect through decrease of the release of noradrenaline in sympathetic nerve endings. The sedative effects are mediated through decreased firing at the locus coeruleus, the predominant noradrenergic nucleus, situated in the brain stem (10). The highly selective affinity for the α₂-adrenoceptor (over the α₁-adrenoceptor) of dexmedetomidine should, in theory, cause less unwanted cardiovascular effects and make dexmedetomidine a preferable agent (11, 12). Although neither clonidine nor dexmedetomidine is licensed for use in pediatric sedation, both are commonly used off label in the PICU, a practice consistent with many other agents prescribed in the PICU environment (13).

A recent Cochrane review of α₂ agonist use in long-term sedation found that dexmedetomidine reduced the duration of mechanical ventilation and length of ICU stay versus traditional regimens; however, the review did not include any pediatric studies (14). We are aware of several studies that have been published in pediatrics in this area in recent years (15–17). The U.S. Food and Drug Administration (FDA) advice has advocated for the use of sedation effectiveness–based outcomes for determination of sedative drug efficacy (18). The reduction in opioid consumption is a conveniently captured outcome and widely reported throughout included studies. Yet, it does not address therapeutic advantage conferred by the administration of α₂ agonists other than lessening exposure to other potentially harmful agents. Adult dexmedetomidine studies have shown noninferiority to both midazolam and propofol based on sedation score measurements, which supports the use of dexmedetomidine in the adult ICU (19). When seeking an alternative to a standard sedative agent, such as midazolam in pediatrics, demonstrating comparable time at target sedation using exclusively, an agent with a more favorable safety profile would be ideal. The objective of this systematic review is to compare PICU patients who received α₂ agonists as part of their sedation regimen with patients who received non-α₂–based sedation regimens in order to compare the proportion of time these patients achieved target sedation score.

**MATERIALS AND METHODS**

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed to conduct this review. Studies were included if they meet the following eligibility criteria: study design: RCTs; population: studies reporting on children who are 18 years old or younger in a PICU/neonatal ICU; intervention: studies reporting on patients exposed to either clonidine or dexmedetomidine for the indication of sedation; comparator: studies with a comparison group of children not exposed to clonidine or dexmedetomidine were included; and outcome: studies reporting on the following outcomes.

**Primary Outcome for Our Review**

Proportion of time at target sedation (%) (measured by a clinical sedation score as a length of time at target sedation/total sedation time).

**Secondary Outcomes for Our Review**

Opioid consumption expressed as morphine equivalents per kilogram per 24 hours where possible; benzodiazepine consumption for α₂ and comparator groups (reported details include the name of benzodiazepine used and the amount of benzodiazepine administered per kilogram per 24 hr expressed as midazolam equivalents where possible); length of mechanical ventilation (time); length of PICU stay (time); adverse events (effect on heart rate and blood pressure). Studies outside the PICU setting were excluded. Indications other than sedation, such as neonatal abstinence syndrome, procedural sedation and regional anesthesia use, were also excluded. No language, publication date, or publication status restrictions were imposed.

**Search Strategy**

A comprehensive electronic literature search was performed using the Cochrane Central Register of Controlled Trials, PubMed (1946–July 2014), EMBASE (1966–July 2014), CINAHL, and LILACS. The final search was performed on July 25, 2014. In addition to electronic searching, reference lists of included studies were also examined. Trial registries (http://www.clinicaltrials.gov and www.controlled-trials.com) were also searched. A sample search strategy is included in Appendix 1.

**Study Selection**

Two reviewers (J.C.H. and M.M.H.) independently screened titles and abstracts of all retrieved studies for inclusion. A full-text review of all potentially relevant citations for inclusion was conducted. Disagreements were resolved by a third reviewer where necessary. The two reviewers met after independently screening the titles/abstracts and full texts to discuss inclusion and exclusion of each article.

**Data Collection and Extraction**

Two researchers piloted a customized data collection tool on Microsoft Excel (Microsoft, Redmond, WA). Data were extracted by one primary researcher (J.C.H.) and checked for accuracy by a second reviewer (M.M.H./G.C.). The authors of included studies were contacted to attain additional information when required.

**Data Items**

**Study Characteristics.** Population: we recorded patient age and patient type, for example, post–cardiac surgery, all at
baseline; intervention: we recorded the type of $\alpha_2$-agonist used, dose, duration of treatment, other analgesia, and sedation used; comparator: type of comparator and dose used; primary outcome: for our primary outcomes, we extracted data on the type of sedation score used and percentage of time at target sedation (%) (i.e., time at target sedation/total time sedated × 100); and secondary outcomes: we extracted data on cumulative opioid use (µg/kg per 24 hr) and converted to morphine equivalents per kilogram per 24 hours where possible. The conversion to morphine equivalents used was morphine 1 mg = fentanyl 15 µg = hydromorphone 0.15 mg. Data were extracted on type and cumulative benzodiazepine use (µg/kg per 24 hr), type and use of rescue sedatives (number of boluses per 24 hr), length of time mechanically ventilated, adverse events (change in blood pressure and heart rate), and length of PICU stay versus comparator group.

Quality of Studies
Additional data: we extracted data to investigate clinical and methodologic heterogeneity across studies. Study quality was assessed using the Cochrane risk of bias tool.

Pooling of Data
Pooling of data was not attempted, and a narrative synthesis is provided.

RESULTS
We identified 4,539 citations, and after removal of duplicates and initial screening, 132 full-text articles were accessed. One hundred twenty-six of these were excluded leaving six RCTs eligible for inclusion (Fig. 1, PRISMA flow diagram).

Three trials reported on clonidine (15–17), and three trials reported on dexmedetomidine (20–22).

RCTs
Study Characteristics. Table 1 describes the six RCTs included in this review. Trials were conducted in Germany (15), the United States (22), Turkey (20), India (21), Canada/England (16), and the United Kingdom (17). The clonidine trials were of intermittent nasogastric boluses (5 µg/kg every 6 hr) and a continuous IV infusion (1 or 3 µg/kg loading followed by 0–3 µg/kg/hr) (15–17). All three dexmedetomidine trials were of continuous IV infusion (20–22). The dexmedetomidine doses varied from 0.25 to 0.5 µg/kg/hr, one with a loading dose (20), one without (21), and one as needed (22).

Risk of Bias. Risk of bias in the RCTs is shown in Figure 2. The clonidine trials were judged to have the lowest risk of bias (15–17). Adequate randomization and blinding of personnel and outcomes were described. However, the included clonidine trials did have factors that may influence validity of results. The multisite clonidine versus placebo study by Hünseler et al (15) had unevenly balanced age cohorts with overrepresentation of neonates that may have affected outcomes. Also, the dosage regimen was determined based on a single-case series (23). The pilot clonidine versus placebo RCT by Duffett et al (16) used a bolus dosage regimen without description of dose justification. No pharmacodynamic analysis was performed to investigate dose response. The clonidine versus midazolam trial by Wolf et al (17) had low risk of bias by design but did involve a large number of major protocol violations. Many violations were
### TABLE 1. Description of Included Studies Assessing Efficacy of $\alpha_2$-Agonists for Sedation

<table>
<thead>
<tr>
<th>Authors</th>
<th>Study Design</th>
<th>Outcomes of Interest</th>
<th>Study Drug</th>
<th>Patient Type</th>
<th>Age of $\alpha_2$-Group</th>
<th>Other Sedation and Analgesia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duffett et al (16), $n = 50$</td>
<td>Multisite RCT</td>
<td>Sedation efficacy: sedation scores (COMFORT and State Behavior Scale) Opioid sparing: morphine equivalents per day Secondary: midazolam equivalents per day, adverse events, duration of ventilation, PICU stay</td>
<td>Intervention ($n = 25$): clonidine 5 $\mu$g/kg 6 hourly nasogastric route; no loading Comparison ($n = 25$): placebo</td>
<td>Mechanically ventilated children 30 d–18 yr</td>
<td>2.7 yr (30 d–17 yr)$^a$</td>
<td>Morphine, midazolam, chloral hydrate, uncontrolled</td>
</tr>
<tr>
<td>Hünseler et al (15), $n = 219$</td>
<td>Multisite RCT</td>
<td>Sedation efficacy: sedation scores (Hartwig and COMFORT scores) Opioid Sparing: fentanyl use ($\mu$g/kg/hr) 1–72 hr after starting medication Secondary: midazolam use ($\mu$g/kg/hr), adverse events, duration of ventilation, PICU stay</td>
<td>Intervention ($n = 105$): clonidine 1 $\mu$g/kg/hr infusion started on day 4 of mechanical ventilation; and no loading Comparison ($n = 114$): placebo</td>
<td>Mechanically ventilated infants under 2 yr</td>
<td>86 ± 146$^b$ 55/105 of clonidine group were neonates</td>
<td>Fentanyl infusion and boluses, midazolam infusion and boluses, thiopentone boluses</td>
</tr>
<tr>
<td>Wolf et al (17), $n = 120$</td>
<td>Multisite RCT</td>
<td>Sedation efficacy: number with &gt; 80% time at target COMFORT score Opioid sparing: maximum doses, time to maximum dose, and supplementary analgesia</td>
<td>Intervention ($n = 61$): clonidine at 3 $\mu$g/kg loading followed by 0–3 $\mu$g/kg/hr Comparison ($n = 59$): midazolam 200 $\mu$g/kg loading followed by 0–200 $\mu$g/kg/hr</td>
<td>Mechanically ventilated children 30 d to 15 yr old</td>
<td>0.6 (0.08–13.85)$^a$ yr</td>
<td>Morphine infusion</td>
</tr>
<tr>
<td>Aydogan et al (20), $n = 32$</td>
<td>Single-site RCT</td>
<td>Sedation efficacy: sedation score (RASS) Opioid sparing: fentanyl consumption and pain scores (VAS) over 24 hr post surgery) Secondary: duration of ventilation, adverse events, and PICU stay</td>
<td>Intervention ($n = 16$): Dexamethasone 0.4 $\mu$g/kg/hr (after loading of 0.25 $\mu$g/kg) Comparison ($n = 16$): midazolam 0.1 mg/kg/hr (after loading of 0.1 mg/kg)</td>
<td>Mechanically ventilated children 12–18 yr post scoliosis surgery</td>
<td>13.6 (12–16)$^a$ yr</td>
<td>Intermittent fentanyl boluses</td>
</tr>
<tr>
<td>Prasad et al (21), $n = 60$</td>
<td>Single-site RCT</td>
<td>Sedation efficacy: sedation scores (Ramsay sedation scale score, PICU sedation score, and tracheal suction score) Opioid sparing: number of rescue fentanyl boluses required Secondary: duration of ventilation and adverse events (systolic and diastolic BPs and HR)</td>
<td>Intervention ($n = 30$): Dex at 0.5 $\mu$g/kg/hr; no loading Comparison ($n = 30$): fentanyl 1 $\mu$g/kg/hr</td>
<td>Children over 1 yr post cardiac surgery</td>
<td>6 ± 4$^a$ yr</td>
<td>Rescue fentanyl bolus</td>
</tr>
<tr>
<td>Tobias et al (22), $n = 30$</td>
<td>Single-site RCT</td>
<td>Sedation efficacy: sedation scores (Ramsay sedation scale score, PICU sedation score, tracheal suctioning score, and bispectral index monitoring) Opioid sparing: number of morphine boluses, total morphine use over 24 hr, and adverse events (HR and BP)</td>
<td>Intervention 1 ($n = 10$): Dex start at 0.25 $\mu$g/kg/hr, (bolus if needed) Intervention 2 ($n = 10$): Dex start at 0.5 $\mu$g/kg/hr (bolus if needed) Comparison ($n = 10$): midazolam 0.1 $\mu$g/kg/hr (bolus if needed)</td>
<td>Mechanically ventilated infants and children, average age 40 mos</td>
<td>44 ± 54$^a$ months in Dex 0.25 $\mu$g/kg/hr group 39 ± 44$^a$ months in Dex 0.5 $\mu$g/kg/hr group</td>
<td>Rescue morphine boluses</td>
</tr>
</tbody>
</table>

$^a$Median (range).

$^b$Mean ± SD.

| RCT = randomized controlled trial, RASS = Richmond Agitation-Sedation Scale, Dex = dexmedetomidine, VAS = Visual Analogue Scale, BP = blood pressure, HR = heart rate. |
related to incorrect medication adjustments in response to sedation score recordings, which may have introduced performance bias. The study was also significantly underpowered, which makes result interpretation difficult (17).

The dexmedetomidine trials were smaller and generally had a higher risk of bias (20–22). The study by Aydogan et al (20) seems to have the lowest risk of bias. Blinding is described for the assessor of sedation levels. However, it was unclear whether the assessor of pain scores, which ultimately decided the opioid consumption, was blinded. This may increase the risk of performance bias (20). Tobias and Berkenbosch (22) did not describe the randomization process or if blinding of assessors took place and seems at risk of selection and performance bias.

Several sedation scales are used across the trials; all three clonidine trials used validated scales. Validated sedation scales for this use are COMFORT/COMFORT behavior scale, the Hartwig sedation scale, and the State Behavior Scale. Hünseler et al (15) used Hartwig and COMFORT, Duffett et al (16) used COMFORT and the State Behavior Scale, and Wolf et al (17) also used the COMFORT score. The Ramsay sedation scale and other PICU scales were used in the dexmedetomidine trials, although these are not validated for the study population (20–22).

**Primary Outcome.** RCT efficacy results are shown in Table 2. Only one of the six included RCTs reported on “proportion of time maintained at target” (17). Wolf et al (17) attempted to demonstrate equivalence of clonidine to midazolam but only recruited 16% of their anticipated 1,000 patients. Both arms had similar proportion of time at optimal sedation (74% and 73%, respectively). Using their chosen primary outcome of proportion of patients with greater than 80% of time adequately sedated, they were unable to demonstrate equivalence, but noninferiority was shown. Inadequate power and the number of major protocol violations necessitate caution in outcome interpretation.

Sedation scores were recorded in all six trials. In the clonidine trial by Hünseler et al (15), neonates, but not older infants, were significantly more sedated in the clonidine group than in the placebo group during the 72-hour observation period as measured by both the Hartwig score and COMFORT score. The clonidine pilot trial by Duffett et al (16) had similar sedation levels between clonidine and placebo as measured by COMFORT and State Behavior Scale, although patient numbers were small ($n = 50$).

Two dexmedetomidine trials describe similar sedation scores to midazolam in mechanically ventilated children (22) and to fentanyl in post–cardiac surgery children (21). The final trial describes a lighter level of sedation with dexmedetomidine compared with fentanyl in post–scoliosis surgery adolescents (20).

**Secondary Outcomes.** Opioid consumption is reported as an outcome in all six trials, and four trials had sufficient information to calculate morphine equivalent per kilogram per 24 hours (Fig. 3, mean difference in morphine equivalents per kilogram per 24 hr in RCTs). Analysis of the clonidine trial by Hünseler et al (15) reports a significant reduction in opioid consumption with clonidine treatment compared with placebo. There is a reduction in fentanyl use of 0.06 morphine equivalents per kilogram per hour (95% CI, 0.01–0.1; morphine equivalents per kilogram per hour) with clonidine. This result is not statistically significant when adjusted for baseline opioid consumption and significant only in neonates. Duffett et al (16) had inadequate power to assess opioid-sparing effects of clonidine.

In the dexmedetomidine studies, two trials described decreased opioid use with exposure to dexmedetomidine (20, 22). The first of these studies was a study that reported on postoperative opioid consumption in scoliosis surgery patients (20). The second study was a study of mechanically ventilated children given dexmedetomidine infusions (a significant decrease in consumption with 0.5 μg/kg/hr infusions but not 0.25 μg/kg/hr infusions) (22). The final trial describes similar rescue opioid requirements in a dexmedetomidine group and a fentanyl infusion group following cardiac surgery (21).

Benzodiazepine usage is reported in two of the RCTs (15, 16). In the clonidine trial by Hünseler et al (15), the neonate clonidine cohort consumed 51.3 μg/kg/hr (95% CI, 10.2–92.3) less midazolam during the study period than the placebo group (15). No overall decrease was seen in the other age cohorts. The pilot trial by Duffett et al (16) showed a nonsignificant decrease in midazolam consumption over 24 hours but was not powered to show a significant difference (16). In the trial by Tobias and Berkenbosch (22), midazolam was only administered to one of the three groups (22). Benzodiazepine-sparing effects are not reported in the other two remaining dexmedetomidine trials (20, 21).
Duration of ventilation as an outcome is confounded by the clinical indication for its use. It is dependent on severity of illness and the use of individual center’s extubation readiness criteria. However, it is of interest for safety and efficacy determination of sedatives. It was reported as an outcome in four of the six trials. In the clonidine trial by Hünseler et al (15), duration of ventilation was similar in the clonidine and placebo groups (15). Duffett et al (16) showed similar length of ventilation in their pilot clonidine study (22). Two dexmedetomidine trials associated dexmedetomidine with statistically shorter duration of ventilation compared with midazolam and fentanyl in postoperative cardiac (131 ± 51 min with dexmedetomidine).

### TABLE 2. Efficacy and Safety Results of Included Studies α<sub>2</sub>-Agonists for Sedation

<table>
<thead>
<tr>
<th>Authors</th>
<th>Time at Target Sedation</th>
<th>Sedation Scores</th>
<th>Opioid-Sparing Effect</th>
<th>Benzodiazepine-Sparing Effect</th>
<th>Duration of Ventilation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duffett et al (16)</td>
<td>NR</td>
<td>↔ Sedation scores similar to placebo (COMFORT and State Behavior Scale)</td>
<td>↔ NS; morphine equivalents (mg/kg/d) 1.3 (0.7–13.6)&lt;sup&gt;a&lt;/sup&gt; with clonidine and 5.8 (0.8–11.6)&lt;sup&gt;a&lt;/sup&gt; with placebo</td>
<td>↔ NS; midazolam equivalents (mg/kg/d), 1.9 (0.9–4.3)&lt;sup&gt;a&lt;/sup&gt; with clonidine and 2.5 (1.6–3.9)&lt;sup&gt;a&lt;/sup&gt; with placebo</td>
<td>↔ NS</td>
</tr>
<tr>
<td>Hünseler et al (15)</td>
<td>NR</td>
<td>↓ Lower sedation scores (more sedated (Hartwig) in the clonidine group in neonates vs placebo neonates&lt;sup&gt;b&lt;/sup&gt;; NS in other age cohorts)</td>
<td>↓ Mean reduction in fentanyl consumption 0.86 µg/kg/hr (95% CI, 0.14–1.57)&lt;sup&gt;b&lt;/sup&gt;; significant only in neonate cohort and NS when adjusted for baseline fentanyl consumption</td>
<td>↓ Neonates had a 51.3 µg/kg/hr (95% CI, 10.2–92.3) greater decrease from baseline than placebo of midazolam consumption; significant only in neonate cohort</td>
<td>↔ NS</td>
</tr>
<tr>
<td>Wolf et al (17)</td>
<td>↔ Clonidine 74% (56–84)&lt;sup&gt;a&lt;/sup&gt; of time and midazolam 73% (64–82)&lt;sup&gt;a&lt;/sup&gt; of time</td>
<td>↔ Clonidine 21/61 (34%) patients adequately sedated &gt; 80% of time compared with 18/59 (31%) in the midazolam group</td>
<td>↓ Decreased frequency of supplementary analgesia in clonidine group&lt;sup&gt;b&lt;/sup&gt;</td>
<td>↓ Decreased frequency of supplementary sedatives in clonidine group&lt;sup&gt;b&lt;/sup&gt;</td>
<td>NR</td>
</tr>
<tr>
<td>Aydogan et al (20)</td>
<td>NR</td>
<td>↑ Lighter sedation in the Dex group (RASS) vs midazolam group, RASS of 1.12 (–1 to +1)&lt;sup&gt;c&lt;/sup&gt; in the Dex group vs midazolam –1.84 (–2 to +2)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>↓ Decrease in fentanyl consumption in the Dex group over 24 hr (124.1 ± 28&lt;sup&gt;d&lt;/sup&gt; vs 165.8 ± 32.8&lt;sup&gt;d&lt;/sup&gt; µg in the midazolam group)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>NR</td>
<td>↓ Dex group 1.8 (1.1–3.5)&lt;sup&gt;e&lt;/sup&gt; vs 3.75 (1.7–8.7)&lt;sup&gt;e&lt;/sup&gt; hr with midazolam&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>Prasad et al (21)</td>
<td>NR</td>
<td>↔ Sedation scores similar (Ramsay sedation score, PICU sedation score, and tracheal suctioning score)</td>
<td>↔ Similar rescue requirements</td>
<td>NR</td>
<td>↓ Time to extubation from cessation of sedative infusion was 2.2 ± 0.9 d in the Dex group vs 6.2 ± 2 d in the fentanyl group&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Tobias et al (22)</td>
<td>NR</td>
<td>↔ NS (Ramsay score, PICU sedation score, tracheal suctioning score)</td>
<td>↓ Significant decrease in rescue morphine boluses between the midazolam group and the Dex 0.5 µg/kg/hr group&lt;sup&gt;f&lt;/sup&gt;; NS for the Dex 0.25 µg/kg/hr group; ↓ statistically significant decrease in 24-hr morphine consumption in both Dex doses vs midazolam&lt;sup&gt;f&lt;/sup&gt;</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

(Continued)
<table>
<thead>
<tr>
<th>Authors</th>
<th>Heart Rate Effects</th>
<th>BP Effects</th>
<th>Other Adverse Effects</th>
<th>Treatment Duration</th>
<th>PICU Stay</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duffett et al (16)</td>
<td>3/25 patients with bradycardia with clonidine 2/25 with placebo</td>
<td>5/25 patients with hypotension with clonidine 2/25 with placebo</td>
<td>NR</td>
<td>≈ 7 d</td>
<td>NS</td>
</tr>
<tr>
<td>Hünseler et al (15)</td>
<td>NS</td>
<td>BP ≈ 3 mm Hg lower in neonates, not in older infants</td>
<td>No difference in serious adverse events between groups</td>
<td>3 d</td>
<td>NS</td>
</tr>
<tr>
<td>Wolf et al (17)</td>
<td>1 event of bradycardia requiring interventions with clonidine vs 3 events with midazolam</td>
<td>7 hypotension events requiring intervention in the clonidine group vs 3 events in midazolam</td>
<td>A higher incidence of inotropic support during the first 12 hr was required for those on clonidine (clonidine 5/45 [11%] vs midazolam 3/52 [6%]) (95% CI, 0.49–7.61)</td>
<td>1.4 ± 1 d of clonidine vs 2.1 ± 1.6 d on midazolam b</td>
<td>NS</td>
</tr>
<tr>
<td>Aydogan, et al (20)</td>
<td>Heart rate significantly lower in the Dex group at all time points (25% [4/16] bradycardia in the Dex group vs 6% [1/16] in the midazolam group)</td>
<td>NS</td>
<td>NR</td>
<td>1 d on study drug then switch to other agent if needed</td>
<td>NS</td>
</tr>
<tr>
<td>Prasad et al (21)</td>
<td>More bradycardia in the Dex group (decrease &lt; 10–15% from baseline); no interventions needed</td>
<td>NS</td>
<td>NR</td>
<td>0.5 d</td>
<td>NR</td>
</tr>
<tr>
<td>Tobias et al (22)</td>
<td>Heart rate lower in Dex groups (midazolam 142 ± 36 b beats/min, Dex 0.25 μg/kg/hr was 122 ± 31 b beats/min; and Dex 0.5 μg/kg/hr was 112 ± 26 b beats/min); one patient was removed from the study because of bradycardia</td>
<td>NS</td>
<td>NR</td>
<td>0.9 ± 0.4 d</td>
<td>NR</td>
</tr>
</tbody>
</table>

NR = not reported, NS = no significant difference reported, Dex = dexmedetomidine, RASS = Richmond Agitation-Sedation Scale, BP = blood pressure.

aMedian (interquartile range).
bMedian (range).
cMean ± sd.
dp < 0.05.
and 373.25 ± 121.4 min in a fentanyl group) and post–scoliosis surgery (107 [65–208] min with dexmedetomidine vs 225 [104–520] min in a midazolam children group (20, 21).

None of the trials included showed an impact of exposure to α₂-agonists on the length of PICU stay.

Adverse Events

Adverse events are described in Table 2. Both agents seem well tolerated with no authors expressing concern with their safety. Clonidine seems to have a dose-related effect on blood pressure but little effect on heart rate (15–17). Conversely, dexmedetomidine is associated with a decreased heart rate but minimal effect on blood pressure (20–22).

DISCUSSION

Insufficient data exist to suggest that α₂-agonists provide a similar or better proportion of time at target sedation than comparative agents. Heterogeneity across study populations and study design prevent pooling of existing studies to allow conclusions on efficacy of α₂-agonists. Only one trial of clonidine was identified, which reported on this outcome; however, it had low recruitment and numerous protocol violations (17). No dexmedetomidine studies reporting on this outcome were identified. The choice not to use this outcome may be because of low uptake and the use of validated sedation scores in the PICU environment, as well as convenience of capture of other outcome measures, such as opioid use.

This review reports that although clonidine has shown potential as an opioid and benzodiazepine-sparing agent in neonates, this benefit has not been shown elsewhere (15). Dexmedetomidine has been shown to be associated with shorter durations of mechanical ventilation in two trials in children following surgery (20, 21). The included studies suggest that both agents are well tolerated. Side effects, namely hypotension with clonidine and decreased heart rate with dexmedetomidine, were predictable and manageable with adequate monitoring in place (15, 16, 20).

Adequately powered RCTs reporting on sedation-based outcomes are needed; however, this review highlights the current challenges in sedation research in the PICU. The choice of primary outcome is inconsistent across studies. Only one trial used a sedation score–based primary outcome; however, significant underpowering and procedural difficulties with trial conduct make conclusions difficult to determine (17). Several studies also used nonvalidated sedation scales for their population (20, 22). Further barriers to the conduct of trials exist with the lack of evidence-based dosing information for clonidine and lack of an IV formulation in North America.

Clonidine’s dosage regimen remains undefined. Potts et al (24) proposed a bolus of 1 μg/kg, then slow loading over 30 minutes of 2 μg/kg/hr, and then 1 μg/kg/hr for 30 minutes reduced in steps to 0.3 μg/kg/hr maintenance continuous infusion. Wolf et al (17) used 3 μg/kg loading followed by a variable infusion of 0–3 μg/kg/hr. Other pharmacokinetic studies have reported on IV bolus clonidine (25, 26). Dose-finding studies for clonidine are warranted prior to head-to-head comparisons with other sedative agents.

No clonidine formulation has an approved use as a sedative in children. Both oral and IV studies of clonidine use have been included. The choice of route is often dictated by availability of formulations in each country with no suitable IV formulation marketed in North America unlike in Europe. A study of oral bioavailability in children estimates bioavailability at 55%, less than the reported 75–100% in adults (27). This suggests that it would require over twice the IV dose administered orally to achieve equivalent plasma levels. This further highlights the need for dose-finding studies with clonidine.

Dexmedetomidine use has increased significantly over recent years. This is because of a number of factors, including adult efficacy trials, the availability of an IV formulation, and an adult license for use in sedation. Observational studies have advanced dosing strategies for dexmedetomidine now commonly administered at initial doses of approximately 0.4 μg/kg/hr and titrated to ranges of approximately 0.1–2 μg/kg/hr. Loading doses tend not to be used to avoid transient hypertension (28–32).
No study compared clonidine with dexmedetomidine, despite having similar pharmacologic actions and vastly different acquisition prices. The recent availability of generic forms of dexmedetomidine and consequent decreased costs might further alter use patterns of this agent in current practice. Nevertheless, comparative studies would be attractive to clinicians. Clonidine dose-finding studies and development of an age appropriate formulation would permit studies, such as this. The primary outcome measure should be quality of sedation (measured as proportion of time adequately sedated) using a validated clinical sedation scale. The $\alpha_2$-agonists should be compared with a third arm of a current widely used agent, such as midazolam. However, given their widespread use as adjunctive agents to opioid-benzodiazepine regimens, a likely study would be to evaluate whether addition of clonidine or dexmedetomidine can provide an adequate proportion of time adequately sedated without the concurrent escalation of opioids or other sedatives. This would help inform the place of $\alpha_2$-agonists as PICU sedatives, whether they are useful adjunct to lessen benzodiazepine and opioid use, and whether the relative cost difference between agents is justified.

CONCLUSIONS
Although the number of studies on the use of $\alpha_2$-agonists in PICU has increased over the last decade, this review found a lack of robust evidence for either agent as a sedative agent. Sedation-based outcomes are poorly reported. Clonidine has shown potential opioid-sparing effects in neonates and dexmedetomidine in post-surgery children. Dose-finding studies for both clonidine and dexmedetomidine should be prerequisites prior to further research.

REFERENCES
APPENDIX 1. Examples of Detailed Search Strategy Used to Identify Included Studies

Search on July 25, 2014

PubMed
[Dexmedetomidine OR clonidine OR adrenergic alpha-agonists] AND [sedat* OR analgesi* OR pain] AND [child* OR paediatrics OR pediatr* OR infant]

EMBASE
[clonidine OR dexmedetomidine] AND [sedation OR analgesia] AND [child OR infant OR Pediatric Care OR p#ediatr* OR child*]

CINAHL
[clonidine OR dexmedetomidine OR adrenergic alpha-agonists] AND [Pain OR postoperative Pain OR analgesi* OR sedat*] AND [child OR infant OR Pediatric Care OR p#ediatr* OR child*]

LILACS
Clonidine AND child
Dexmedetomidine AND child$