Dexmedetomidine: the new all-in-one drug in paediatric anaesthesia?

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Purpose of review
Dexmedetomidine is a drug with sedative, anxiolytic, sympatholytic and analgesic properties, which is finding widespread practice in paediatric anaesthesia and related practices. The present review summarizes its pharmacology and current experience with the drug.

Recent findings
Dexmedetomidine is proving useful in many diverse areas in paediatric anaesthesia where its sedative properties are useful for premedication, fibreoptic intubation and radiologic procedures. Its use as an adjunct for balanced anaesthesia where it can decrease the use of other drugs, reduce emergence delirium, postoperative shivering and vomiting. Muted apoptotic neuroprotective effects may realize benefits in neonates. Cardiac conduction delay, an adverse effect, may prove beneficial for arrhythmias after congenital cardiac surgery.

Summary
Most of the paediatric published studies concerning dexmedetomidine are observational in nature, with limited control groups or comparators. Adverse effects (e.g. bradycardia) still require greater scrutiny in the paediatric population and particularly with respect to different age groups. Dexmedetomidine currently has a firm position in the armamentarium of anaesthesia pharmacology. It is not the new all-in-one drug, but it is shaping up as a valuable adjunct for diverse indications within paediatric anaesthesia.

Video abstract
http://links.lww.com/COAN/A44.

Keywords
α_2 adrenoceptor agonist, anaesthesia, children, pharmacology

INTRODUCTION

Dexmedetomidine is a selective α_2-agonist. It is in the same class as clonidine but differs from clonidine in that its affinity for α_2-compared with α_1-adrenoreceptors is eight-fold greater. An advantage is that it may be administered by intravenous, intramuscular, subcutaneous, nasal, buccal, rectal and oral routes.

The α_2-adrenoreceptors are located ubiquitously throughout the body with effects that include sedation, anxiolysis and analgesia. Heart rate slows by blocking the cardio-accelerator nerves and by augmenting vagal activity. This α_2-agonist action on the autonomic ganglia includes decreasing sympathetic outflow, which leads to hypotension. Actions on the peripheral vasculature depend on the concentration of dexmedetomidine: vasodilatation is the result of sympatholysis at low concentrations and vasoconstriction is the result of direct action on smooth muscle vasculature at high concentrations. Other manifestations of α_2-adrenoreceptors include inhibition of shivering and promoting diuresis, although the mechanisms by which these are affected remain elusive [1,2]. Consequently dexmedetomidine use in neonates and children has expanded to include prevention of emergence delirium, postoperative pain management, invasive and noninvasive procedural sedation and the management of opioid withdrawal [3–11]. Is this drug the new all-in-one drug for paediatric anaesthesia?

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KEY POINTS

- Dexmedetomidine, a relatively recent drug in the field of paediatric anaesthesia, has raised great interest because of its sedative property without respiratory compromise.
- It could be less damaging to the developing brain than other anaesthesia drugs currently used.
- It seems particularly well suited for painless procedures that require a motionless patient (e.g., radiology procedures, fibreoptic intubation) or procedures that would benefit from nonsupressed cortical activity (e.g., electroencephalographic studies or epilepsy surgery).
- The drug is often cited as one of choice for cardiac surgery, notably for its antiarrythmogenic and postoperative sedation properties, although superiority over other drugs currently used has yet to be demonstrated.
- Although effective to treat many common situations in paediatric anaesthesia such as postoperative delirium, shivering, nausea and vomiting, use of dexmedetomidine is more an adjunct to the current therapies than a new gold standard.

PHARMACODYNAMICS

Dexmedetomidine has effects on cerebral, respiratory, analgesic and cardiovascular systems.

Sedation

Dexmedetomidine provides sedation that permits arousal with gentle stimulation [12]. A plasma concentration in excess of 0.6 μg/l is estimated to produce satisfactory sedation in adult ICU patients [13], and similar target concentrations are estimated in postoperative children after cardiac surgery who require sedation in the intensive care unit [14].

Respiration

The lack of respiratory depression distinguishes this sedative from opioids, benzodiazepines and other sedatives. Although dexmedetomidine blunts the CO_2 response curve [15], it does not lead to extreme hypoxia or hypercapnia. Indeed, respiratory rate, CO_2 tension, and oxygen saturation are generally maintained during dexmedetomidine sedation in children [11,12,16–18].

Anaesthesia

The MAC-sparing effect of isoflurane or sevoflurane in adults using dexmedetomidine is concentration dependent; estimated up to 50% at dexmedetomidine 0.7 μg/l [19–21]. Premedication with intranasal dexmedetomidine (1 and 2 μg/kg) in children 3–7 years decreased the MAC required for tracheal intubation using sevoflurane by 20 and 35%, respectively [22]. Similar results have been reported when infusion (0.5 and 1 μg/kg/h) were continued after an intravenous bolus (1 and 2 μg/kg) [23].

The propofol dose required for sedation and induction of anaesthesia is reduced in the presence of dexmedetomidine in adults [24,25]. The concomitant use of dexmedetomidine (0.5 μg/kg/h) in adolescents undergoing spinal fusion reduced propofol infusion requirements (71 SD 11 μg/kg/min) when compared with those (12–21 years) receiving only propofol and remifentanil (101 SD 33 μg/kg/min) [26].

Dexmedetomidine is often used as an adjunct to other drugs to improve sedation or anaesthesia, for example when added to midazolam it assists achievement of a motionless state for MRI [11,27,28]. Total intravenous anaesthesia with dexmedetomidine and ketamine in children is described [29]. This combination has also been administered as premedication for children 3–6 years using a nebulizer [30▪]. Combined nebulized dexmedetomidine (1 μg/kg) and ketamine (1 mg/kg) proved more effective than either dexmedetomidine 2 μ/kg or ketamine 2 mg/kg.

Analgesia

Several adult [2,31,32] and paediatric [33▪] studies have demonstrated that dexmedetomidine spares opioid requirements during surgery. Effect is short lived after surgery. A meta-analysis of perioperative analgesic effect in children, infants, and neonates showed intraoperative dexmedetomidine administration was associated with reduced postoperative opioid consumption in the postanaesthetic care unit (PACU) [risk ratio (RR) = 0.31; 95% confidence interval (CI), 0.17–0.59], decreased pain intensity (standardized mean difference = −1.18; 95% CI, −1.88 to −0.48] but had no effect upon postoperative nausea and vomiting (RR = 0.67; 95% CI, 0.41–1.08). The optimal bolus dose was 0.5 μg/kg or more [34▪▪]. Although effective after short duration anaesthesia (e.g., myringotomy) [35], recovery may be delayed [36].

Cardiovascular

Dexmedetomidine decreases heart rate in a dose-dependent manner in children [12,19,37–40]. Decreasing the dose of dexmedetomidine restores the heart rate to normal values [41]. With very large doses of dexmedetomidine (2–3 μg/kg over 10 min followed by 1.5–2 μg/kg/h), 12 children under 6 years of age experienced heart rates less than

50 beats/min, although their blood pressures were maintained [39]. Administration of anticholinergics or other medications to increase the heart rate have not been required, but it should be noted that severe and persistent hypertension has been reported when glycopyrrolate was used to treat high-dose dexmedetomidine-induced bradycardia [42].

There are conflicting data regarding its safety in children with congenital heart disease [43–46]. Sinus node and atrioventricular nodal function are both depressed. This adverse effect may be useful for control of supraventricular arrhythmias.

THE CLINICAL MULTIPURPOSE DRUG

The diverse effects that characterize dexmedetomidine pharmacodynamics have been harnessed for a number of purposes in paediatric anaesthesia and fields associated with our specialty.

Sedation

Early use for sedation was almost exclusively with the intravenous route. An initial bolus of 0.5 μg/kg over 10–15 min was followed by an infusion of 0.5–1 μg/kg/h. These regimens were associated with less delirium and tachycardia, lower blood pressure and fewer ventilator days when compared to midazolam in the adult intensive care environment [47▪,48].

Dosing regimens are currently more liberal as practitioners either titrate drug to effect or add supplemental drugs to improve effect. Although undoubtedly effective, dose-finding studies and studies with sedation score-based outcomes in children are still needed for both clonidine and dexmedetomidine [49▪]. Certainly experience in infants and neonates (age < 36 months, $n = 187$) with congenital heart disease and pulmonary arterial hypertension is less convincing than adult reports showing advantages over midazolam. However, neonates and infants given dexmedetomidine required fewer sedative or analgesic drugs and had a lower incidence of delirium than those given midazolam [50]. Comparisons with clonidine are few, despite widespread use of that drug in intensive care [51,52,53▪▪].

Dexmedetomidine sedation outside the operating room is increasing. A review of 13 072 children (ASA 1 or 2) sedated using dexmedetomidine reported an adverse event rate of 3.6% (95% CI, 3.3–3.9%). Airway obstruction was the most common adverse event (0.27%; 95% CI, 0.19–0.37%). Sedation was successful in 99.7% of children [54▪▪]. Although concerns about the effect of bradycardia associated with dexmedetomidine exist, the use of a prophylactic anticholinergic (atropine or glycopyrrolate) showed no advantage in children other than a transient increase in heart rate and systolic blood pressure. Further, anticholinergics may precipitate transient exaggerated systolic blood pressure changes in children given dexmedetomidine [55▪▪].

A meta-analysis comparing dexmedetomidine and propofol in children ($n = 337$) undergoing sedation for MRI demonstrated dexmedetomidine increased the recovery time by 10.7 min (95% CI, 4.3–17.1) [56▪]. Discharge readiness may be slightly delayed but the importance of this in children who are obliged to be monitored for a requisite time after sedation, regardless of sedative agent, is debated [57]. The nasal route has gained popularity in the radiology suite because of ease of administration, reliable effectiveness and ability to administer further doses or supplement with other sedative drugs [58▪]. Intranasal dexmedetomidine (2.5 μg/kg) was found to be superior to oral midazolam (0.5 mg/kg) for producing satisfactory sedation for commuted tomography (CT) imaging [59▪▪]. When used as rescue therapy after failure of chloral hydrate (50 mg/kg), the ED_{50} of intranasal dexmedetomidine for rescue sedation was 0.4 μg/kg in children aged 1–6 months, 0.5 μg/kg in children aged 7–12 months, 0.9 μg/kg in children aged 13–24 months and 1.0 μg/kg in children aged 25–36 months [60▪]. Higher doses in those children 1–6 months age caused increased sedation in a dose-dependent manner [61▪].

Intranasal administration (2.5–3 μg/kg with a repeat dose of 1–1.5 μg/kg if needed 30 min later) is also finding use for electroencephalogram and auditory brain response testing. Onset time was 25 min [interquartile range (IQR), 20–32 min] and the median duration of sedation was 107 min (IQR, 90–131 min) [62▪]. Others have reported similar results with a larger single dose (4 μg/kg) [63▪,64▪]. Aerosolized intranasal dexmedetomidine 2.5–3.0 μg/kg offered satisfactory conditions for transthoracic echocardiography in children (3 months to 3 years) [65▪▪] and was comparable to chloral hydrate 70 mg/kg [66]. The mean wake up time after dexmedetomidine 3 μg/kg was 44.3 min (range 12–123 min) [67▪].

The indications for the use of dexmedetomidine sedation are increasing as familiarity with the drug increases, for example cardiac catheterization [68], craniectomy radiosurgery [69–71,72▪] and even those children with preexisting respiratory problems [73,74]. Use in children suffering burns using doses of dexmedetomidine with a median infusion dose of 0.57 μg/kg/h (range 0.11–1.17 μg/kg/h) was well tolerated and effective [75], but higher doses have proved problematic because of hypotension.

A bolus dose of dexmedetomidine (1.0 μg/kg for 10 min) and high infusion rates (0.7–2.5 μg/kg/h) may require fluid resuscitation or vasopressor support to maintain normotension in critically injured paediatric burn patients [76]. There remains a lack of information about relative recovery times after infusion with this drug compared to others using validated, objective measures that are reproducible form one institution to another.

Awake fibreoptic intubation

Drugs or combinations of drugs with anxiolytic and analgesic properties are popular to facilitate awake fibreoptic intubation; benzodiazepines, propofol, opioids, α2-adrenoceptor agonists and ketamine are commonly used. Dexmedetomidine 1.5 μg/kg has proven effective for awake fiberoptic intubation in adults [77]. Augmentation with ketamine, a drug known for its airway protection properties, also offers advantages in adults [78]. Paediatric practitioners are no strangers to this approach [79].

Premedication

Sedative premedication has long been used in paediatric practice. The cynical older generation of practitioners might suggest that a third of premedicants administered work well, a third have some variable success and that a third fail. Midazolam retains popularity despite criticisms concerning amnesia, confusion and long-term behavioural disturbances [80]. The α2-adrenoceptor agonist, clonidine, has long been advocated as an alternative premedicant [81]. Dexmedetomidine is now competing for that role [82▪]. Onset time after oral administration (4 μg/kg) is slower than midazolam 0.75 mg/kg (18.9 SD 3.7 vs. 30.5 SD 4.4 min) [83▪]. Modest dose comparisons (midazolam 0.5 mg/kg, dexmedetomidine 2 μg/kg) in children (3.96 SD 2.04 years) presenting for cardiac surgery were equally effective. [84▪] However, a meta-analysis ($n = 1033$ children) comparing dexmedetomidine to midazolam reported a higher incidence of satisfactory sedation at separation from parents (74 vs. 50%, RR = 1.30), a reduced incidence of postoperative agitation (10 vs. 40%, RR = 0.31), and a reduction in the rescue doses of analgesic drugs (20 vs. 39%, RR = 0.52) [85]. Dexmedetomidine was also superior for providing satisfactory intravenous cannulation compared to placebo [86▪]. Part of dexmedetomidine's appeal as a premedicant is the ability to administer the drug intranasally [87–89].

Balanced anaesthesia

The traditional trilogy of sedation, analgesia and neuromuscular blockade can be refined with the introduction of dexmedetomidine to the mix, allowing reduction of analgesia or sedative requirements. This can be advantageous in spinal instrumentation surgery where inhaled anaesthetic vapours or propofol can lessen the value of neurophysiological evoked potential monitoring. Dexmedetomidine added to a propofol infusion in adolescents (14–18 years) reduced propofol requirements by more than 50%, provided moderate hypotension, decreased blood loss, and allowed monitoring of motor and somatosensory evoked potentials [90]. Similarly, the addition of a dexmedetomidine 1–2 μg/kg before propofol administered for MRI sedation resulted in fewer sedation-related adverse events, particularly upper airway obstruction [91].

Dexmedetomidine (0.5 μg/kg over 10 min, followed by an infusion 0.5 μg/kg/h) in children 1–6 years undergoing cardiac surgery reduced sevoflurane requirements and decreased the incidence of emergence delirium [92▪]. A meta-analysis confirmed a shorter length of postoperative mechanical ventilation, lower postoperative and morphine requirements, reduced stress responses, and lower risk of delirium. Dexmedetomidine increased the bradycardia and hypotension risk [odds ratio (OR) = 3.14; 95% CI, 1.47–6.69] [93].

The addition of ketamine to either propofol [94,95] or dexmedetomidine offers analgesia, better airway protection and greater cardiovascular stability than either drug alone. Fewer oxygen desaturations and a higher rate of successful completion of drug-induced sleep endoscopy were reported in children suffering obstructive sleep apnoea when a combination of dexmedetomidine and ketamine was used compared to propofol alone [96]. Although both combinations ketamine–dexmedetomidine and ketamine–midazolam offered effective sedation–analgesia without causing noteworthy adverse effects in children undergoing burns dressing changes, the former resulted in higher sedation and less hemodynamic discrepancy [97]. Low-dose intravenous ketamine 0.15 mg/kg followed by dexmedetomidine 0.3 μg/kg reduced the incidence and severity of emergence agitation in children (3–7 years) undergoing adenotonsillectomy following sevoflurane-based anaesthesia and provided smooth extubation [98].

Current evidence does not substantiate any clinically significant interaction between dexmedetomidine and neuromuscular blockade [99].

Apoptotic neuroprotection

Dexmedetomidine was not associated with neuroapoptosis or other neurodegenerative effects in animal studies involving infant rodents and foetal

primates [100,101]. It also attenuated isoflurane-induced neurocognitive impairment in neonatal rats [102▪▪]. It may have detrimental effects on the brain, but those areas affected differ from other drugs. Although ketamine caused cellular degeneration and apoptosis in limbic brain regions, dexmedetomidine produced cellular degeneration and apoptosis in primary sensory brain regions of rat pups [103]. The bulk of current evidence suggests fewer consequences attributable to α2-agonists than most other anaesthetic drugs. Consequently, the drug is being explored in animal models for possible use in neonates who have suffered perinatal asphyxia. Its neuroprotective, analgesic, anti-inflammatory and sympatholytic properties that may be beneficial when combined with therapeutic hypothermia [104,105,106▪▪].

Dexmedetomidine is also being explored as an alternative sedative in neonates requiring surgery using caudal blockade. A pilot study of dexmedetomidine (2 μg/kg over 10 min, followed by 1 μg/kg over the next 10 min) sedation enabled caudal placement within 20 min with subsequent inguinal hernia repair [107]. A current infant study investigating sevoflurane neurotoxicity is using dexmedetomidine as the comparator (ClinicalTrials.gov Identifier: NCT02353182).

PONV

Ondansetron and dexamethasone remain the pillars of antiemetic therapy in paediatric anaesthesia. A meta-analysis from adults who underwent gynaecological surgery showed that dexmedetomidine was superior to placebo in attenuating the incidence of postoperative shivering, pruritus and pain scores. There was a reduction in the need for an antiemetic (RR = 0.62; 95% CI, 0.39–0.99) [108▪▪]. However, this effect may be related to a lower consumption of intraoperative opioids, rather than specific antiemetic activity [109]. Paediatric studies are lacking.

Emergence delirium

Emergence delirium occurs commonly after most inhalational anaesthetics in children [110▪]. A number of medications have been shown to attenuate the incidence of delirium after anaesthesia, including both clonidine and dexmedetomidine [8,111,112▪]; odds ratio for dexmedetomidine are estimated at 0.18 (95% CI, 0.12–0.25), for clonidine 0.25 (95% CI, 0.14–0.46) and for propofol 0.32 (95% CI, 0.18–0.56) [113]. Dexmedetomidine decreased the incidence of agitation after sevoflurane anaesthesia: after an infusion of dexmedetomidine (0.2 μg/kg/h), recovery was not prolonged [114], whereas a single intravenous dose of 0.5 μg/kg, 5 min before the end of surgery, may prolong recovery [115▪,116]. Unfortunately results are inconsistent [117–119] and depend on factors such as anaesthetic agents, analgesic delivery, age, delirium scoring system, time of assessment, underlying disorder and type of surgery. Clonidine, for example, may have minimal impact in children with good analgesia after adenotonsillectomy [120]. A higher dose of intravenous dexmedetomidine (1 μg/kg) is more effective than lower doses after strabismus surgery [121▪], whereas nasal dexmedetomidine 1–2 μg/kg is effective after cataract surgery [122▪] and ambulatory surgery in children 3–7 years [123].

Shivering after anaesthesia

No drug is effective enough to be considered the gold standard for the management of postoperative shivering. Dexmedetomidine 1 μg/kg has some action compared to placebo on cold-induced shivering in adults,[124] but so does relaxation, breath holding and mental arithmetic [125▪]. An adult meta-analysis showed a decrease in postanaesthetic shivering for those given dexmedetomidine (RR = 0.27; 95% CI, 0.19–0.36). Similar results are reported in children [126]. Although onset of effect is relatively fast (3.5 SD 0.9 min) after dexmedetomidine 0.5 μg/kg infused over 5 min [127], dexmedetomidine is no better than other drugs that have been used (e.g., tramadol) [128].

Opioid withdrawal

Clonidine remains popular for the management of opioid and benzodiazepine withdrawal symptoms in paediatric intensive care. There is a growing body of literature describing the use of dexmedetomidine in adults for this purpose. Evidence supporting such use in children is mostly anecdotal [7,129]. Regimens such as loading dose of 0.5–1.0 μg/kg administered over 5–10 min, followed by a continuous infusion at 0.1–1.4 μg/kg/h for a period of 1–16 days have been proposed [130].

One reservation is the fear of a withdrawal from dexmedetomidine itself after prolonged use (>24 h). Up to 80% of children (0–17 years) in an intensive care experienced withdrawal symptoms after infusion (0.42 SD 0.17 μg/kg/h) [131▪▪,132▪]. Prospective, controlled studies are needed to characterize the safety of long-term dexmedetomidine therapy in critically ill children [131▪▪].

Epilepsy studies

Sedation for electroencephalography in uncooperative children is contentious because many

sedatives, hypnotics and general anaesthetics interfere with brain electrical activity [133]. Dexmedetomidine sedation elicited an EEG pattern similar to that of stage II sleep with modest increases in theta, alpha and beta activity and the drug has been advocated as a suitable sedative in these children [134]. However, both chloral hydrate and dexmedetomidine induce similar electroencephalographic changes [133].

Suppression of cortical electrical activity by the drugs used in anaesthesia and monitored by electrocorticogram is a major concern during epilepsy surgery. The use of dexmedetomidine enhanced or did not alter spike rate in young adults undergoing anterior temporal lobe resection with amygdalo-hippocampectomy for drug-resistant mesial temporal lobe epilepsy [135].

Table 1. Unanswered questions about dexmedetomidine

Is the drug neuroprotective or nontoxic to the developing human brain?
What dose regimen for an opioid–dexmedetomidine mixture is well tolerated and effective in neonates?
What shape are the concentration–response curves for sedation, analgesia and anxiolysis?
What is the concentration–response relationship for adverse effects (e.g. bradycardia, hypotension, cardiac conduction)?
How does interaction with other drugs impact on effect and safety?
Is dexmedetomidine better than currently used drugs for many of its indications (e.g. sedation, emergence delirium, withdrawal symptoms and local anaesthesia adjuncts)?
What is the impact of age on both desired and undesired effects?
Dexmedetomidine is commonly used with other drugs. What is the full nature of these drug interactions when used for differing indications?

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Junctional ectopic tachycardia

Junctional ectopic tachycardia (JET) can prolong the duration of mechanical ventilation and stay in the intensive care unit after cardiac surgery. Amiodarone is often used as the antiarrhythmic of choice, and can also be used to decrease the incidence of postoperative JET when used prophylactically [136]. Dexmedetomidine may be an alternative antiarrhythmic drug [137▪,138,139]. Larger prospective studies are still required before the position of this drug for this context can be sure [140]. The risk for bradycardia and/or atrioventricular nodal dysfunction associated with its use must be balanced against therapeutic advantages [141▪].

The use of dexmedetomidine may be undesirable during electrophysiology studies [43], although dexmedetomidine did not interfere with the conduct of paediatric electrophysiological studies for SVT and the successful ablation of such arrhythmias; this despite a greater need for isoproterenol when dexmedetomidine was used [142▪]. Uncertainty exists about the possibility that dexmedetomidine may prolong the QT interval on the electrocardiogram and/or induce Torsades de Pointes [143].

Regional blockade

The use of adjunct drugs in combination with local anaesthetics for neuraxial blockade both prolong block duration and improve block quality. Clonidine has direct central effects and has been long used as the preferred adjunct [144▪▪]. Dexmedetomidine has higher lipid solubility and is finding increasing use as an alternative to clonidine [145].

There is widespread use of dexmedetomidine to supplement local anaesthetics for paediatric caudal blockade. Although these studies demonstrate better pain scores compared to fentanyl [146], fewer adverse effects [147▪,148], prolongation of block duration [148,149▪], dose optimization at 1 μg/kg [150▪] and superiority of the single shot caudal route over the intravenous route [151], comparative data with clonidine are rare. A meta-analysis ($n = 328$) concluded longer duration of caudal analgesia compared to local anaesthesia alone (mean difference 8.21 h; 95% CI, 5.02–11.40) [152].

α2 adrenoceptor agonists together with local anaesthetics prolong the duration of peripheral nerve blockade. Whether this is a systemic effect or a local effect remains debated. Early exploratory data suggests that the use of dexmedetomidine as an adjunct to an ilioinguinal nerve block results in lower pain scores and less emergence agitation after paediatric inguinal hernia repair [153▪]. A meta-analysis in children ($n = 283$, age: 0.8–13 years, weight 8–47 kg) determined block duration was prolonged with the use of α_2-adrenoreceptor agonists (9.75 vs. 3.75 h) compared to the use of plain local anaesthetics, that supplemental analgesics were reduced and that no serious adverse effects were evident. That meta-analysis did not provide specific support for dexmedetomidine over clonidine [154▪▪].

CONCLUSION

Dexmedetomidine is proving useful in many diverse areas in paediatric anaesthesia. α2 receptors are certainly important in this field of medicine but have previously not been seen as the answer to so many vexing anaesthesia issues. Clonidine may be equally effective for some indications and monetary costs are far less. The shorter elimination half-life of dexmedetomidine may be beneficial in some

situations, and less useful in others. Unfortunately most of the published studies concerning dexmedetomidine are observational in nature, with limited control groups or comparators. Additional research in children is required before recommendations can be made regarding appropriate dosing, drug interactions and adverse effects (Table 1) [43,155, 156,157▪]. Dexmedetomidine currently has a firm position in the armamentarium of anaesthesia pharmacology. It is not the new all-in-one drug, but it is shaping up as a valuable adjunct for diverse indications within paediatric anaesthesia.

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Conflicts of interest

There are no conflicts of interest.

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

- ▪ of special interest
- ▪▪ of outstanding interest

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27. Heard CM, Joshi P, Johnson K. Dexmedetomidine for pediatric MRI sedation: a review of a series of cases. Pediatr Anesth 2007; 17:888–892.
28. Luscri N, Tobias JD. Monitored anesthesia care with a combination of ketamine and dexmedetomidine during magnetic resonance imaging in three children with trisomy 21 and obstructive sleep apnea. Pediatr Anesth 2006; 16:782–786.
29. Goyal R. Total intravenous anesthesia with dexmedetomidine and ketamine in children. Pediatr Anesth 2015; 25:756–757.
30. ▪ Zanaty OM, El Metainy SA. A comparative evaluation of nebulized dexmedetomidine, nebulized ketamine, and their combination as premedication for outpatient pediatric dental surgery. Anesth Analg 2015; 121:167–171.

A novel method of administration that takes advantage of the high bioavailability with the nasal route. The additive effect reduces dose of each drug lessens the individual adverse effects.

31. Hall JE, Uhrich TD, Barney JA, *et al.* Sedative, amnestic, and analgesic properties of small-dose dexmedetomidine infusions. Anesth Analg 2000; 90:699–705.
32. Arain SR, Ruehlow RM, Uhrich TD, *et al.* The efficacy of dexmedetomidine versus morphine for postoperative analgesia after major inpatient surgery. Anesth Analg 2004; 98:153–158.
33. ▪ Sun Y, Ye H, Xia Y, *et al.* Clinical efficacy of dexmedetomidine in the diminution of fentanyl dosage in pediatric cardiac surgery. Minerva Pediatrica 2017; 69:181–187.

Cardiac anaesthesia using a lower dose of fentanyl 15 μg/kg when augmented with dexmedetomidine was as effective as fentanyl 30 μg/kg. Unfortunately, a dose-response relationship for fentanyl alone was not explored. The use of lower fentanyl doses (10 μg/kg) without dexmedetomidine is now commonly used in recipes designed for early extubation.

34. ▪▪ Bellon M, Le Bot A, Michelet D, *et al.* Efficacy of intraoperative dexmedetomidine compared with placebo for postoperative pain management: a meta-analysis of published studies. Pain Ther 2016; 5:63–80.

A review of 14 randomized trials demonstrating dexmedetomidine (>0.5 μg/kg) administration in children reduces postoperative opioids consumption and postoperative pain in postanaesthetic care unit (PACU). Impact on analgesia beyond PACU or effect of subsequent dexmedetomidine dosing requires further investigation.

35. Dewhirst E, Fedel G, Raman V, *et al.* Pain management following myringotomy and tube placement: intranasal dexmedetomidine versus intranasal fentanyl. Int J Pediatr Otorhinolaryngol 2014; 78:1090–1094.
36. Pestieau SR, Quezado ZM, Johnson YJ, *et al.* The effect of dexmedetomidine during myringotomy and pressure-equalizing tube placement in children. Pediatr Anesth 2011; 21:1128–1135.
37. Ebert TJ, Hall JE, Barney JA, *et al.* The effects of increasing plasma concentrations of dexmedetomidine in humans. Anesthesiology 2000; 93:382–394.
38. Mason KP, Zurakowski D, Zgleszewski SE, *et al.* High dose dexmedetomidine as the sole sedative for pediatric MRI. Pediatr Anesth 2008; 18:403–411.
39. Mason KP, Zurakowski D, Zgleszewski S, *et al.* Incidence and predictors of hypertension during high-dose dexmedetomidine sedation for pediatric MRI. Pediatr Anesth 2010; 20:516–523.

40. Berkenbosch JW, Tobias JD. Development of bradycardia during sedation with dexmedetomidine in an infant concurrently receiving digoxin. Pediatr Crit Care Med 2003; 4:203–205.
41. Mason KP, Zgleszewski S, Forman RE, *et al.* An exaggerated hypertensive response to glycopyrrolate therapy for bradycardia associated with high-dose dexmedetomidine. Anesth Analg 2009; 108:906–908.
42. Hammer GB, Drover DR, Cao H, *et al.* The effects of dexmedetomidine on cardiac electrophysiology in children. Anesth Analg 2008; 106:79–83.
43. Barton KP, Munoz R, Morell VO, *et al.* Dexmedetomidine as the primary sedative during invasive procedures in infants and toddlers with congenital heart disease. Pediatr Crit Care Med 2008; 9:612–615.
44. Easley RB, Tobias JD. Pro: dexmedetomidine should be used for infants and children undergoing cardiac surgery. J Cardiothorac Vasc Anesth 2008; 22:147–151.
45. Hammer GB. Con: dexmedetomidine should not be used for infants and children during cardiac surgery. J Cardiothorac Vasc Anesth 2008; 22:152–154.
46. Riker RR, Shehabi Y, Bokesch PM, *et al.* Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial. JAMA 2009; 301:489–499.
47. ▪ Reade MC, Eastwood GM, Bellomo R, *et al.* Effect of dexmedetomidine added to standard care on ventilator-free time in patients with agitated delirium: a randomized clinical trial. JAMA 2016; 315:1460–1468.

An adult study pointing to benefits from sedation using dexmedetomidine in intensive care. Among patients with agitated delirium receiving mechanical ventilation in the intensive care unit, the addition of dexmedetomidine to standard care compared with standard care alone (placebo) resulted in more ventilator-free hours at 7 days. The trial used standard care rather than comparators such as midazolam, clonidine or propofol. Extrapolation of these results to children remains uncertain.

48. Hayden JC, Breatnach C, Doherty DR, *et al.* Efficacy of α2-agonists for sedation in pediatric critical care: a systematic review. Pediatr Crit Care Med 2016; 17:e66–75.
49. ▪ Jiang L, Ding S, Yan H, *et al.* A retrospective comparison of dexmedetomidine versus midazolam for pediatric patients with congenital heart disease requiring postoperative sedation. Pediatr Cardiol 2015; 36:993–999.

A retrospective review suggesting a lower incidence of emergence delirium in infants less than 36 months given fentanyl/dexmedetomidine rather than midazolam/dexmedetomidine. Results may not be as impressive as reported because emergence delirium scores were low and assessment in neonates is difficult.

50. Pohl-Schickinger A, Lemmer J, Hubler M, *et al.* Intravenous clonidine infusion in infants after cardiovascular surgery. Pediatr Anesth 2008; 18:217–222.
51. Hanning SM, Orlu Gul M, Toni I, *et al.* A mini-review of nonparenteral clonidine preparations for paediatric sedation. J Pharm Pharmacol 2017; 69:398–405.
52. Arenas-Lopez S, Mulla H, Manna S, *et al.* Enteral absorption and haemodynamic response of clonidine in infants postcardiac surgery. Br J Anaesth 2014; 113:964–969.
53. ▪▪ Sulton C, McCracken C, Simon HK, *et al.* Pediatric procedural sedation using dexmedetomidine: a report from the pediatric sedation research consortium. Hosp Pediatr 2016; 6:536–544.

This is an important paper documenting dexmedetomidine sedation practice in the United States. The paediatric providers responsible for sedation were anaesthetists (35%), intensivists (34%), emergency medicine physicians (12.7%), hospitalists (1.1%) and others (17%). Adverse event rates were quantified (3.6%; 95% CI, 3.3–3.9%). Airway obstruction was the most common serious adverse event (0.27%; 95% CI, 0.19–0.37%). The sedation success rate was very high (99.7%), regardless of provider.

54. ▪▪ Subramanyam R, Cudilo EM, Hossain MM, *et al.* To pretreat or not to pretreat: prophylactic anticholinergic administration before dexmedetomidine in pediatric imaging. Anesth Analg 2015; 121:479–485.

Concerns about bradycardia trouble most practitioners when using dexmedetomidine. Some use an anticholinergic prophylactically to prevent this adverse effect. This study demonstrated that administration of a prophylactic anticholinergic had no advantage other than a transient clinically insignificant increase in heart rate and systolic blood pressure. Further, it may precipitate transient exaggerated blood pressure changes.

55. ▪▪ Fang H, Yang L, Wang X, *et al.* Clinical efficacy of dexmedetomidine versus propofol in children undergoing magnetic resonance imaging: a meta-analysis. Int J Clin Exp Med 2015; 8:11881–11889.

Propofol is considered by many as the gold standard sedative agent. This meta-analysis comprised only five trials ($n = 337$) pronounced propofol superior to dexmedetomidine. Those given dexmedetomidine had similar durations of sedation but increased the recovery time and increased paediatric anaesthesia emergence delirium scores. These effects do not negate the usefulness of dexmedetomidine, particularly because of its airway safety and high bioavailability using alternative routes of administration (e.g. nasal).

56. ▪ Phelps JR, Russell A, Lupa MC, *et al.* High-dose dexmedetomidine for noninvasive pediatric procedural sedation and discharge readiness. Pediatr Anesth 2015; 25:877–882.

The authors suggest that discharge times after procedural sedation at their institution (79–101 min) were longer than those reported by others. However, arousal time and hospital discharge times are different measures. Institutional discharge guidelines differ between facilities. Arousal is dependent on dose administered. The manuscript does remind readers that dexmedetomidine has a half-life of 2 h; it takes three to five half-lives to clear.

57. Mekitarian Filho E, Robinson F, de Carvalho WB, *et al.* Intranasal dexmedetomidine for sedation for pediatric computed tomography imaging. J Pediatr 2015; 166:1313–1315; e1311.
58. ▪ Ghai B, Jain K, Saxena AK, *et al.* Comparison of oral midazolam with intranasal dexmedetomidine premedication for children undergoing CT imaging: a randomized, double-blind, and controlled study. Pediatr Anesth 2017; 27:37–44.

Intranasal dexmedetomidine 2.5 μg/kg proved better than oral midazolam 0.5 mg/kg for CT sedation. Although these are common clinical doses, bioequivalence is not proven, absorption characteristics differ between drugs, clearances and concentration time profiles are dissimilar A higher dose of midazolam, for example, may have been more effective.

59. ▪▪ Zhang W, Fan Y, Zhao T, *et al.* Median effective dose of intranasal dexmedetomidine for rescue sedation in pediatric patients undergoing magnetic resonance imaging. Anesthesiology 2016; 125:1130–1135.

This paper and the one below explore the use of intranasal dexmedetomidine rescue after failed chloral hydrate sedation for MRI. The ED_{50} increases with advancing age during the first 3 years of life, increasing from 0.4 μg/kg in children aged 1-6 months, to 1.0 μg/kg in children aged 25-36 months.

60. ▪ Zhang W, Wang Z, Song X, *et al.* Comparison of rescue techniques for failed chloral hydrate sedation for magnetic resonance imaging scans - additional chloral hydrate vs intranasal dexmedetomidine. Pediatr Anesth 2016; 26:273–279.

Intranasal dexmedetomidine is easy to administer and a useful adjunct when chloral hydrate (50 mg/kg) fails to adequately sedate for MRI. The authors noted that rescue dexmedetomidine 2 μg/kg increased time to arousal after the scan when compared to 1 μg/kg.

61. ▪ Baier NM, Mendez SS, Kimm D, *et al.* Intranasal dexmedetomidine: an effective sedative agent for electroencephalogram and auditory brain response testing. Pediatr Anesth 2016; 26:280–285.

This review documents the effectiveness of intranasal dexmedetomidine for EEG or auditory brain response (ABR) testing. An initial dose of 2.5-3 μg/kg was given with a repeat dose of 1-1.5 μg/kg if needed 30 min later. Time to onset of sleep was 25 min with duration of sedation 107 min. Avoidance of intravenous injection is a major benefit for many children

62. ▪ Reynolds J, Rogers A, Capehart S, *et al.* Retrospective comparison of intranasal dexmedetomidine and oral chloral hydrate for sedated auditory brainstem response exams. Hosp Pediatr 2016; 6:166–171.

A retrospective review showing intranasal dexmedetomidine, like chloral hydrate, provides effective sedation for ABR examinations, with the benefits of an ability to begin the test sooner and complete the examination with a single dose, in addition to a decreased incidence of hypoxemia. The question of superiority of one drug over the other remains hanging.

63. ▪ Reynolds J, Rogers A, Medellin E, *et al.* A prospective, randomized, double-blind trial of intranasal dexmedetomidine and oral chloral hydrate for sedated auditory brainstem response (ABR) testing. Pediatr Anesth 2016; 26:286–293.

A follow-on study to the one above where completion rates for ABR with a single dose of dexmedetomidine (3 μg/kg) were higher than those given chloral hydrate (50 mg/kg). The time to successful testing start was shorter for dexmedetomidine and the proportion of children whose parents reported a return to baseline activity on the day of testing was also greater. Better understanding of the usefulness of these two drugs could be made if dose-response or concentration-response curves for each drug were characterized.

64. ▪ Miller JW, Divanovic AA, Hossain MM, *et al.* Dosing and efficacy of intranasal dexmedetomidine sedation for pediatric transthoracic echocardiography: a retrospective study. Can J Anaesth 2016; 63:834–841.

This retrospective study found aerosolized intranasal dexmedetomidine offers satisfactory conditions for transthoracic echocardiography in children 3 months to 3 years of age with an optimal dose of 2.5-3.0 μg/kg administered under the supervision of a paediatric cardiac anaesthesiologist.

65. ▪▪ Miller J, Xue B, Hossain M, *et al.* Comparison of dexmedetomidine and chloral hydrate sedation for transthoracic echocardiography in infants and toddlers: a randomized clinical trial. Pediatr Anesth 2016; 26:266–272.

This is a follow-up study to the retrospective review above. The authors report intranasal dexmedetomidine 2 and 3 μg/kg were found to be as effective for TTE sedation as oral chloral hydrate 70 mg/kg with similar sedation onset and recovery time and heart rate changes. The dose of chloral hydrate was larger than other sedative study comparisons that used 50 mg/kg.

66. Li BL, Ni J, Huang JX, *et al.* Intranasal dexmedetomidine for sedation in children undergoing transthoracic echocardiography study - a prospective observational study. Pediatr Anesth 2015; 25:891–896.
67. ▪ Cetin M, Birbicer H, Hallioglu O, *et al.* Comparative study between the effects of dexmedetomidine and propofol on cerebral oxygenation during sedation at pediatric cardiac catheterization. Ann Card Anaesth 2016; 19:20–24.

Concerns that hypotension and bradycardia or vasoconstriction caused by dexmedetomidine may reduce cerebral tissue oxygenation appear unfounded.

68. Sheshadri V, Chandramouli BA. Pediatric awake craniotomy for seizure focus resection with dexmedetomidine sedation - a case report. J Clin Anesth 2016; 32:199–202.
69. Fahy CJ, Okumura M. Sedation for paediatric stereotactic radiosurgery: the dexmedetomidine experience. Anaesth Intens Care 2004; 32:809–811.
70. Grant R, Gruenbaum SE, Gerrard J. Anaesthesia for deep brain stimulation: a review. Curr Opin Anaesth 2015; 28:505–510.

71. Everett LL, van Rooyen IF, Warner MH, *et al.* Use of dexmedetomidine in awake craniotomy in adolescents: report of two cases. Pediatr Anesth 2006; 16:338–342.

72. ▪ Najafi N, Veyckemans F, Van de Velde A, *et al.* Usability of dexmedetomidine for deep sedation in infants and small children with respiratory morbidities. Acta Anaesthesiol Scand 2016; 60:865–873.

Children with respiratory morbidities are at increased risk of developing adverse respiratory events, even with dexmedetomidine. Data from this retrospective review demonstrate that dexmedetomidine deep sedation was well tolerated in children with significant respiratory morbidities. Moreover, children younger than 1 year of age were administered lower dexmedetomidine dose than children older than 1 year of age for the same sedation level, consistent with reduced clearance in that age group

73. Enomoto Y, Kudo T, Saito T, *et al.* Prolonged use of dexmedetomidine in an infant with respiratory failure following living donor liver transplantation. Pediatr Anesth 2006; 16:1285–1288.

74. Lin H, Faraklas I, Sampson C, *et al.* Use of dexmedetomidine for sedation in critically ill mechanically ventilated pediatric burn patients. J Burn Care Res 2011; 32:98–103.

75. Shank ES, Sheridan RL, Ryan CM, *et al.* Hemodynamic responses to dexmedetomidine in critically injured intubated pediatric burned patients: a preliminary study. J Burn Care Res 2013; 34:311–317.

76. Dhasmana SC. Nasotracheal fiberoptic intubation: patient comfort, intubating conditions and hemodynamic stability during conscious sedation with different doses of dexmedetomidine. J Maxillofac Oral Surg 2014; 13:53–58.

77. Sinha SK, Joshiraj B, Chaudhary L, *et al.* A comparison of dexmedetomidine plus ketamine combination with dexmedetomidine alone for awake fiberoptic nasotracheal intubation: a randomized controlled study. J Anaesthesiol Clin Pharmacol 2014; 30:514–519.

78. Iravani M, Wald SH. Dexmedetomidine and ketamine for fiberoptic intubation in a child with severe mandibular hypoplasia. J Clin Anesth 2008; 20:455–457.

79. Bergendahl H, Lonnqvist PA, Eksborg S. Clonidine in paediatric anaesthesia: review of the literature and comparison with benzodiazepines for premedication. Acta Anaesthesiol Scand 2006; 50:135–143.

80. Nishina K, Mikawa K, Shiga M, *et al.* Clonidine in paediatric anaesthesia. Pediatr Anesth 1999; 9:187–202.

81. Sidhu GK, Jindal S, Kaur G, *et al.* Comparison of intranasal dexmedetomidine with intranasal clonidine as a premedication in surgery. Indian J Pediatr 2016; 83:1253–1258.

82. ▪ Jannu V, Mane RS, Dhorigol MG, *et al.* A comparison of oral midazolam and oral dexmedetomidine as premedication in pediatric anesthesia. Saudi J Anaesth 2016; 10:390–394.

This prospective, randomized, controlled study in 60 children, aged 1-7 years showed premedication with oral dexmedetomidine 4 μg/kg produced equally effective preoperative sedation and a better recovery from anaesthesia in comparison to oral midazolam 0.75 mg/kg The dose of both drugs differ from other similar studies, highlighting our lack of dose equivalence understanding.

83. ▪ Faritus SZ, Khazaee-Koohpar M, Ziyaeifard M, *et al.* Oral dexmedetomidine versus midazolam as anesthetic premedication in children undergoing congenital heart surgery. Anesth Pain Med 2015; 5:e25032.

Another study comparing midazolam (0.5 mg/kg) and dexmedetomidine (2 μg/kg) PO; similar results were reported in each group, although acceptance of a mask at induction was better in those given dexmedetomidine.

84. ▪ Pasin L, Febres D, Testa V, *et al.* Dexmedetomidine vs midazolam as preanesthetic medication in children: a meta-analysis of randomized controlled trials. Pediatr Anesth 2015; 25:468–476.

Meta-analyses enable large numbers to be assessed in order to tease out which is the better premedicant. This analysis suggests dexmedetomidine is effective in decreasing anxiety upon separation from parents, decreasing postoperative agitation, and providing more effective postoperative analgesia when compared with midazolam. Such studies disregard dose of each drug, a common failing. However, dexmedetomidine does seem to have a slight edge over midazolam, some of which may be attributed to its analgesic effect.

85. Peng K, Wu SR, Ji FH, *et al.* Premedication with dexmedetomidine in pediatric patients: a systematic review and meta-analysis. Clinics (Sao Paulo, Brazil) 2014; 69:777–786.

86. ▪ Bhat R, Santhosh MC, Annigeri VM, *et al.* Comparison of intranasal dexmedetomidine and dexmedetomidine-ketamine for premedication in pediatrics patients: a randomized double-blind study. Anesth Essays Res 2016; 10:349–355.

The addition of ketamine 2 mg/kg to intranasal dexmedetomidine 1 μg/kg had little premedicant impact.

87. Surendar MN, Pandey RK, Saksena AK, *et al.* A comparative evaluation of intranasal dexmedetomidine, midazolam and ketamine for their sedative and analgesic properties: a triple blind randomized study. J Clin Pediatr Dent 2014; 38:255–261.

88. Talon MD, Woodson LC, Sherwood ER, *et al.* Intranasal dexmedetomidine premedication is comparable with midazolam in burn children undergoing reconstructive surgery. J Burn Care Res 2009; 30:599–605.

89. Ibraheim OA, Abdulmonem A, Baaj J, *et al.* Esmolol versus dexmedetomidine in scoliosis surgery: study on intraoperative blood loss and hemodynamic changes. Middle East J Anaesthesiol 2013; 22:27–33.

90. Boriosi JP, Eickhoff JC, Klein KB, *et al.* A retrospective comparison of propofol alone to propofol in combination with dexmedetomidine for pediatric 3T MRI sedation. Pediatr Anesth 2017; 27:52–59.

91. Sun Y, Liu J, Yuan X, *et al.* Effects of dexmedetomidine on emergence delirium in pediatric cardiac surgery. Minerva Pediatrica 2017; 69:165–173.

92. ▪ Pan W, Wang Y, Lin L, *et al.* Outcomes of dexmedetomidine treatment in pediatric patients undergoing congenital heart disease surgery: a meta-analysis. Pediatr Anesth 2016; 26:239–248.

This meta-analysis showed dexmedetomidine was associated with shorter length of mechanical ventilation, lower postoperative fentanyl and morphine requirements, reduced stress response and lower risk of delirium. Dexmedetomidine caused an increase the bradycardia and hypotension risk. Unfortunately results rely on data from observational studies and randomized controlled trials are few.

93. Coulter FL, Hannam JA, Anderson BJ. Ketofol dosing simulations for procedural sedation. Pediatr Emerg Care 2014; 30:621–630.

94. Coulter FL, Hannam JA, Anderson BJ. Ketofol simulations for dosing in pediatric anesthesia. Pediatr Anesth 2014; 24:806–812.

95. Kandil A, Subramanyam R, Hossain MM, *et al.* Comparison of the combination of dexmedetomidine and ketamine to propofol or propofol/sevoflurane for drug-induced sleep endoscopy in children. Pediatr Anesth 2016; 26:742–751.

96. Gunduz M, Sakalli S, Gunes Y, *et al.* Comparison of effects of ketamine, ketamine-dexmedetomidine and ketamine-midazolam on dressing changes of burn patients. J Anaesthesiol Clin Pharmacol 2011; 27:220–224.

97. Hadi SM, Saleh AJ, Tang YZ, *et al.* The effect of KETODEX on the incidence and severity of emergence agitation in children undergoing adenotonsillectomy using sevoflurane based-anesthesia. Int J Pediatr Otorhinolaryngol 2015; 79:671–676.

98. Talke PO, Caldwell JE, Richardson CA, *et al.* The effects of dexmedetomidine on neuromuscular blockade in human volunteers. Anesth Analg 1999; 88:633–639.

99. Sanders RD, Sun P, Patel S, *et al.* Dexmedetomidine provides cortical neuroprotection: impact on anaesthetic-induced neuroapoptosis in the rat developing brain. Acta Anaesthesiol Scand 2010; 54:710–716.

100. Koo E, Oshodi T, Meschter C, *et al.* Neurotoxic effects of dexmedetomidine in fetal cynomolgus monkey brains. J Toxicol Sci 2014; 39:251–262.

101. Sanders RD, Xu J, Shu Y, *et al.* Dexmedetomidine attenuates isoflurane-induced neurocognitive impairment in neonatal rats. Anesthesiology 2009; 110:1077–1085.

102. ▪▪ Pancaro C, Segal BS, Sikes RW, *et al.* Dexmedetomidine and ketamine show distinct patterns of cell degeneration and apoptosis in the developing rat neonatal brain. J Matern Fetal Neonatal Med 2016; 29:3827–3833.

It appears increasingly clear that all anaesthesia drugs have some effect on cells involved in neurodevelopment. The meaning and the clinical significance of these findings in humans remains to be established. Dexmedetomidine produced significant cellular degeneration and apoptosis in primary sensory brain regions, but nonsignificant changes in limbic regions (as was observed with ketamine). Uncertainty remains about whether this makes dexmedetomidine a better drug than ketamine in human infants.

103. Ezzati M, Broad K, Kawano G, *et al.* Pharmacokinetics of dexmedetomidine combined with therapeutic hypothermia in a piglet asphyxia model. Acta Anaesthesiol Scand 2014; 58:733–742.

104. Pan W, Lin L, Zhang N, *et al.* Neuroprotective effects of dexmedetomidine against hypoxia-induced nervous system injury are related to inhibition of NF-κB/COX-2 pathways. Cell Mol Neurobiol 2016; 36:1179–1188.

105. Wang L, Liu H, Zhang L, *et al.* Neuroprotection of dexmedetomidine against cerebral ischemia-reperfusion injury in rats: involved in inhibition of NF-κB and inflammation response. Biomol Ther (Seoul) 2016; https://doi.org/10.4062/biomolther.2015.180.

106. ▪▪ Bong CL, Yeo AS, Fabila T, *et al.* A pilot study of dexmedetomidine sedation and caudal anesthesia for inguinal hernia repair in infants. Pediatr Anesth 2016; 26:621–627.

Dexmedetomidine has not been implicated in anaesthesia-induced neurotoxicity and may be neuroprotective in preclinical studies. Consequently, investigators are exploring regional blockade with sedation using dexmedetomidine in infants. This pilot study demonstrates that such anaesthesia is possible for uncomplicated hernia surgery. It provides a road map that others can use to improve the technique.

107. Zhong WG, Ge XY, Zhu H, *et al.* Dexmedetomidine for antiemesis in gynecologic surgery: a meta-analysis of randomized controlled trials. Int J Clin Exp Med 2015; 8:14566–14576.

108. ▪▪ Liang X, Zhou M, Feng JJ, *et al.* Efficacy of dexmedetomidine on postoperative nausea and vomiting: a meta-analysis of randomized controlled trials. Int J Clin Exp Med 2015; 8:12113–12134.

Meta-analysis ($n = 6480$) was used to assess the efficacy of dexmedetomidine on PONV in adults. An antiemetic effect can only be achieved with dexmedetomidine more than 0.5 μg/kg intravenously, but effect was similar to that of widely used agents, such as propofol or midazolam. Although dexmedetomidine was superior to placebo, much of its antiemetic effect may be related to a reduced consumption of intraoperative opioids.

109. Belleville JP, Ward DS, Bloor BC, *et al.* Effects of intravenous dexmedetomidine in humans. I. Sedation, ventilation, and metabolic rate. Anesthesiology 1992; 77:1125–1133.

110. ■ Rosen HD, Mervitz D, Cravero JP. Pediatric emergence delirium: Canadian Pediatric Anesthesiologists' experience. Pediatr Anesth 2016; 26:207–212.

This survey of Canadian Pediatric Anaesthesiologists revealed that total intravenous anaesthesia (TIVA) was considered by 38% of respondents as a good technique used to prevent emergence delirium. Medications used for treatment included propofol (42%), midazolam (31%), fentanyl (10%), morphine (7%), and dexmedetomidine (5%), with 87% of respondents rating effectiveness of treatment as 'usually works quickly with one dose'. The survey highlights the need for further investigation.

111. Wang W, Huang P, Gao W, *et al.* Efficacy and acceptability of different auxiliary drugs in pediatric sevoflurane anesthesia: a network meta-analysis of mixed treatment comparisons. Sci Rep 2016; 6:36553.

112. ■ Wang X, Deng Q, Liu B, *et al.* Preventing emergence agitation using ancillary drugs with sevoflurane for pediatric anesthesia: a network meta-analysis. Mol Neurobiol 2016; DOI: 10.1007/s12035-016-0229-0. [Epub ahead of print]

The authors argue that incorporating a drug that reduces emergence delirium into an anaesthetic that uses sevoflurane is better than treating emergence agitation when it occurs postoperatively. Dexmedetomidine ranked highly compared to other drugs such as fentanyl, sufentanil, ketamine, clonidine, remifentanil, propofol, and midazolam.

113. Shukry M, Clyde MC, Kalarickal PL, *et al.* Does dexmedetomidine prevent emergence delirium in children after sevoflurane-based general anesthesia? Pediatr Anesth 2005; 15:1098–1104.

114. Guler G, Akin A, Tosun Z, *et al.* Single-dose dexmedetomidine reduces agitation and provides smooth extubation after pediatric adenotonsillectomy. Pediatr Anesth 2005; 15:762–766.

115. ■ Makkar JK, Bhatia N, Bala I, *et al.* A comparison of single dose dexmedetomidine with propofol for the prevention of emergence delirium after desflurane anaesthesia in children. Anaesthesia 2016; 71:50–57.

Dexmedetomidine 0.3 μg/kg reduced the incidence of emergence delirium after infra-umbilical surgery but this was at the expense of a greater incidence of sedation in the recovery period. These results are a little surprising given the low dose of dexmedetomidine used; they point to the need for a dose response relationship to be characterized.

116. Cao JL, Pei YP, Wei JQ, *et al.* Effects of intraoperative dexmedetomidine with intravenous anaesthesia on postoperative emergence agitation/delirium in paediatric patients undergoing tonsillectomy with or without adenoidectomy: A CONSORT-prospective, randomized, controlled clinical trial. Medicine (Baltimore) 2016; 95:e5566.

117. Hauber JA, Davis PJ, Bendel LP, *et al.* Dexmedetomidine as a rapid bolus for treatment and prophylactic prevention of emergence agitation in anesthetized children. Anesth Analg 2015; 121:1308–1315.

118. Liu Y, Kang DL, Na HY, *et al.* Consequence of dexmedetomidine on emergence delirium following sevoflurane anesthesia in children with cerebral palsy. Int J Clin Exp Med 2015; 8:16238–16244.

119. Blackburn L, Ottaway K, Anderson BJ. The impact of clonidine on sedation after adenotonsillectomy: a prospective audit. Pediatr Anesth 2014; 24:1268–1273.

120. Song IA, Seo KS, Oh AY, *et al.* Dexmedetomidine injection during strabismus surgery reduces emergence agitation without increasing the oculocardiac reflex in children: a randomized controlled trial. PLoS One 2016; 11:e0162785.

121. ■ Lin Y, Chen Y, Huang J, *et al.* Efficacy of premedication with intranasal dexmedetomidine on inhalational induction and postoperative emergence agitation in pediatric undergoing cataract surgery with sevoflurane. J Clin Anesth 2016; 33:289–295.

Strabismus surgery is associated with a high incidence of emergence delirium. The use of nasal dexmedetomidine as a premedicant was associated with reduced emergence delirium in PACU. Comparative data with other drugs are lacking.

122. ■ Mukherjee A, Das A, Basunia SR, *et al.* Emergence agitation prevention in paediatric ambulatory surgery: a comparison between intranasal Dexmedetomidine and Clonidine. J Res Pharm Pract 2015; 4:24–30.

Intranasal dexmedetomidine 1 μg/kg was more effective than clonidine 4 μg/kg in decreasing the incidence and severity of EA, when administered 45 min before the induction of anaesthesia with sevoflurane for paediatric day care surgery. Interpretation of these data is difficult; an understanding of dose-response relationships for each drug would help.

123. Callaway CW, Elmer J, Guyette FX, *et al.* Dexmedetomidine reduces shivering during mild hypothermia in waking subjects. PLoS One 2015; 10:e0129709.

124. Israel DJ, Wittmers LE, Hoffman RG, *et al.* Suppression of shivering by breath holding, relaxation, mental arithmetic, and warm water ingestion. Aviat Space Environ Med 1993; 64:1108–1112.

125. ■ Liu ZX, Xu FY, Liang X, *et al.* Efficacy of dexmedetomidine on postoperative shivering: a meta-analysis of clinical trials. Can J Anaesth 2015; 62:816–829.

While dexmedetomidine was effective to reduce shivering after anaesthesia, its effect was similar to other widely used antishivering agents, such as fentanyl, meperidine, tramadol or clonidine.

126. Blaine Easley R, Brady KM, Tobias JD. Dexmedetomidine for the treatment of postanesthesia shivering in children. Pediatr Anesth 2007; 17:341–346.

127. Sahi S, Singh MR, Katyal S. Comparative efficacy of intravenous dexmedetomidine, clonidine, and tramadol in postanesthesia shivering. J Anaesthesiol Clin Pharmacol 2016; 32:240–244.

128. Vega L, Sanchez-de-Toledo J, Gran F, *et al.* Prevention of opioid withdrawal syndrome after pediatric heart transplantation: usefulness of dexmedetomidine. Rev Esp Cardiol (Engl Ed) 2013; 66:593–595.

129. Oschman A, McCabe T, Kuhn RJ. Dexmedetomidine for opioid and benzodiazepine withdrawal in pediatric patients. Am J Health Syst Pharm 2011; 68:1233–1238.

130. Carney L, Kendrick J, Carr R. Safety and effectiveness of dexmedetomidine in the pediatric intensive care unit (SAD-PICU). Can J Hosp Pharm 2013; 66:21–27.

131. ■■ Takahashi Y, Ueno K, Ninomiya Y, *et al.* Potential risk factors for dexmedetomidine withdrawal seizures in infants after surgery for congenital heart disease. Brain Dev 2016; 38:648–653.

This paper is concerning because dexmedetomidine is increasingly used for sedation after cardiac surgery in children. Physicians should be aware dexmedetomidine use in these infants has potential to cause withdrawal seizures accompanied by preceding pyrexia after discontinuation of dexmedetomidine. Higher cumulative dose and abrupt discontinuation of dexmedetomidine appears to increase the risk for these withdrawal seizures.

132. ■ Fernandes ML, Oliveira WM, Santos Mdo C, *et al.* Sedation for electroencephalography with dexmedetomidine or chloral hydrate: a comparative study on the qualitative and quantitative electroencephalogram pattern. J Neurosurg Anesthesiol 2015; 27:21–25.

The differences of dexmedetomidine and chloral hydrate in EEG power did not change the EEG qualitative interpretation, which was similar with the two drugs. Other studies comparing natural sleep and sleep induced by these drugs are needed to clarify the clinical relevance of the observed EEG quantitative differences.

133. Mason KP, O'Mahony E, Zurakowski D, *et al.* Effects of dexmedetomidine sedation on the EEG in children. Pediatr Anesth 2009; 19:1175–1183.

134. Chaitanya G, Arivazhagan A, Sinha S, *et al.* Dexmedetomidine anesthesia enhances spike generation during intra-operative electrocorticography: a promising adjunct for epilepsy surgery. Epilepsy Res 2015; 109:65–71.

135. Imamura M, Dossey AM, Garcia X, *et al.* Prophylactic amiodarone reduces junctional ectopic tachycardia after tetralogy of Fallot repair. J Thorac Cardiovasc Surg 2012; 143:152–156.

136. Kadam SV, Tailor KB, Kulkarni S, *et al.* Effect of dexmeditomidine on postoperative junctional ectopic tachycardia after complete surgical repair of tetralogy of Fallot: a prospective randomized controlled study. Ann Card Anaesth 2015; 18:323–328.

137. ■ El-Shmaa NS, El Amrousy D, El Feky W. The efficacy of preemptive dexmedetomidine versus amiodarone in preventing postoperative junctional ectopic tachycardia in pediatric cardiac surgery. Ann Card Anaesth 2016; 19:614–620.

Perioperative use of dexmedetomidine or amiodarone infusion was associated with a lower incidence of JET as compared to placebo in children 2-18 years. These data suggest an alternative management to amiodarone. It would be useful to know if these results can be reproduced in younger children (<2 years), a higher risk group, undergoing tetralogy of Fallot repair.

138. Rajput RS, Das S, Makhija N, *et al.* Efficacy of dexmedetomidine for the control of junctional ectopic tachycardia after repair of tetralogy of Fallot. Ann Pediatr Cardiol 2014; 7:167–172.

139. Shuplock JM, Smith AH, Owen J, *et al.* Association between perioperative dexmedetomidine and arrhythmias after surgery for congenital heart disease. Circ Arrhythm Electrophysiol 2015; 8:643–650.

140. Ergul Y, Unsal S, Ozyilmaz I, *et al.* Electrocardiographic and electrophysiologic effects of dexmedetomidine on children. Pacing Clin Electrophysiol 2015; 38:682–687.

141. ■ Tirotta CF, Nguyen T, Fishberger S, *et al.* Dexmedetomidine use in patients undergoing electrophysiological study for supraventricular tachyarrhythmias. Pediatr Anesth 2017; 27:45–51.

The conduction and sinus node effects caused by dexmedetomidine have resulted in reluctance to use this drug during electrophysiological studies in children. Tirotta *et al.* conclude, that dexmedetomidine does not interfere with the conduct of electrophysiological studies for SVT and the successful ablation of such arrhythmias. It did however result in a greater need for isoproterenol.

142. ■ Gorges M, Whyte SD, Sanatani S, *et al.* Changes in QTc associated with a rapid bolus dose of dexmedetomidine in patients receiving TIVA: a retrospective study. Pediatr Anesth 2015; 25:1287–1293.

Dexmedetomidine is listed as a medication with possible risk of prolonging the QT interval and/or inducing Torsades de Pointes. In this study, a rapid bolus of dexmedetomidine transiently shortened corrected QT intervals, contrary to expectations. However, these effects are confounded by dexmedetomidine-induced bradycardia. This observation warrants further investigation.

143. Lonnqvist PA. Adjuncts should always be used in pediatric regional anesthesia. Pediatr Anesth 2015; 25:100–106.

144. ■■ Zhang C, Li C, Pirrone M, *et al.* Comparison of dexmedetomidine and clonidine as adjuvants to local anesthetics for intrathecal anesthesia: a meta-analysis of randomized controlled trials. J Clin Pharmacol 2016; 56:827–834.

This meta-analysis compared dexmedetomidine to clonidine as an intrathecal adjunct in adults. There was a slight difference in onset of sensory block (40 s) The duration of stable sensory block, duration of overall sensory block, and the time before the need for analgesic requirements were extended, 10.8, 22.3 and 38.6 min, respectively, when dexmedetomidine was used as an adjuvant to local anaesthetics Compared to clonidine, the addition of dexmedetomidine as an adjuvant to local anaesthetics was associated with earlier, prolonged sensory block characteristics and later need for analgesic requirements. A similar study is required for children.

145. Jarineshin H, Fekrat F, Kargar Kermanshah A. Treatment of postoperative pain in pediatric operations: comparing the efficiency of bupivacaine, bupivacaine-dexmedetomidine and bupivacaine-fentanyl for caudal block. Anesth pain Med 2016; 6:e39495.

146. Kamal M, Mohammed S, Meena S, *et al.* Efficacy of dexmedetomidine as an adjuvant to ropivacaine in pediatric caudal epidural block. Saudi J Anaesth 2016; 10:384–389.

147. ■ Goyal V, Kubre J, Radhakrishnan K. Dexmedetomidine as an adjuvant to bupivacaine in caudal analgesia in children. Anesth Essays Res 2016; 10:227–232.

The mean duration of effective analgesia in those children undergoing infraumbilical surgery given dexmedetomidine as an adjunct (9.9 SD 0.9 h) was twice that of those without (4.3 SD 1.0 h). Although postoperative pain scores are reported less in those given dexmedetomidine, the clinical difference is minor. Similar results were posted by Kamal *et al.* [146].

148. Fares KM, Othman AH, Alieldin NH. Efficacy and safety of dexmedetomidine added to caudal bupivacaine in pediatric major abdominal cancer surgery. Pain Physician 2014; 17:393–400.

149. ■ Al-Zaben KR, Qudaisat IY, Abu-Halaweh SA, *et al.* Comparison of caudal bupivacaine alone with bupivacaine plus two doses of dexmedetomidine for postoperative analgesia in pediatric patients undergoing infra-umbilical surgery: a randomized controlled double-blinded study. Pediatr Anesth 2015; 25:883–890.

The authors report 1 μg/kg caudal dexmedetomidine achieved comparable prolongation of postoperative analgesia to 2 μg/kg dose, with shorter duration of postoperative sedation and lower incidence of other side effects.

150. ■ Al-Zaben KR, Qudaisat IY, Alja'bari AN, *et al.* The effects of caudal or intravenous dexmedetomidine on postoperative analgesia produced by caudal bupivacaine in children: a randomized controlled double-blinded study. J Clin Anesth 2016; 33:386–394.

Debate exists about whether effects of caudal dexmedetomidine are systemic or local. These authors noted that compared to IV administration, caudal administration of dexmedetomidine during caudal bupivacaine anaesthesia provided prolonged postoperative analgesia and a greater analgesic sparing effect without significant adverse effects. This suggests a greater role of neuraxial compared to that of peripheral α_2-adrenoreceptors in pain processing.

151. Tong Y, Ren H, Ding X, *et al.* Analgesic effect and adverse events of dexmedetomidine as additive for pediatric caudal anesthesia: a meta-analysis. Pediatr Anesth 2014; 24:1224–1230.

152. Garg R, Rao S, John C, *et al.* Extubation in the operating room after cardiac surgery in children: a prospective observational study with multidisciplinary coordinated approach. J Cardiothorac Vasc Anesth 2014; 28:479–487.

153. ■ Lundblad M, Marhofer D, Eksborg S, *et al.* Dexmedetomidine as adjunct to ilioinguinal/iliohypogastric nerve blocks for pediatric inguinal hernia repair: an exploratory randomized controlled trial. Pediatr Anesth 2015; 25:897–905.

This single centre study noted that the use of dexmedetomidine as an adjunct to lioinguinal or iliohypogastric block resulted in less pain during early recovery following paediatric inguinal hernia repair. In addition, the use of adjunct dexmedetomidine was associated with a prolongation of the period to first supplemental analgesia demand.

154. ■■ Lundblad M, Trifa M, Kaabachi O, *et al.* α2 adrenoceptor agonists as adjuncts to peripheral nerve blocks in children: a meta-analysis. Pediatr Anesth 2016; 26:232–238.

This is a follow-up study to the one above. Although raw data from only five studies were gathered and aggregated, this meta-analysis provides evidence-based support for the use of adjunct α2 adrenoceptor agonists when performing peripheral nerve blocks in children. Block duration was significantly prolonged (9.75 vs. 3.75 h) compared to the use of plain local anaesthetic.

155. Hammer GB, Sam WJ, Chen MI, *et al.* Determination of the pharmacodynamic interaction of propofol and dexmedetomidine during esophagogastroduodenoscopy in children. Pediatr Anesth 2009; 19:138–144.

156. Heard C, Burrows F, Johnson K, *et al.* A comparison of dexmedetomidine-midazolam with propofol for maintenance of anesthesia in children undergoing magnetic resonance imaging. Anesth Analg 2008; 107:1832–1839.

157. ■ Cravero J, Anderson B, Wolf A. Whither dexmedetomidine? Pediatr Anesth 2015; 25:868–870.

This is an editorial pointing out the faults of many of the current studies that laud dexmedetomidine. The authors list suggestions for future studies that may improve our knowledge of this drug and how best to use it clinically.