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SYSTEMATIC REVIEW

A systematic review of dexmedetomidine pharmacology in pediatric patients

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Abstract

Dexmedetomidine is a centrally acting alpha-2 agonist used for initiation and maintenance of procedural sedation and mechanical ventilation in adult and pediatric settings. It is commonly used in both pediatric and neonatal intensive care units. Dexmedetomidine requires extensive titration, and patients can be over or under-sedated during titration, leading to adverse events such as hypotension and bradycardia, or inadequate sedation, which can result in self-extubation. There is a critical need to identify factors that contribute to variation in metabolism, clearance, and downstream targets of dexmedetomidine so that individualized pediatric dosing regimens can be developed. This review is focused on dexmedetomidine pharmacokinetics and pharmacodynamics in the pediatric population and dexmedetomidine-related pharmacogenes in both adults and children. We found that the strongest predictors of dexmedetomidine pharmacokinetics were age and size. Multiple pharmacogenes of significance have been identified, including *ADRA2A*, *UGT2B10*, *UGT1A4*, *CYP1A2*, *CYP2A6*, and *CYP2D6*. Evidence is weak for the correlation of these individual polymorphic genes with dexmedetomidine pharmacokinetics/dynamics, though there may be a polygenetic influence on pharmacologic response. This review provides a comprehensive overview of the genomic data gathered to date. We aim to summarize current pharmacologic studies regarding dexmedetomidine use and pharmacology in pediatric patients.

Abbreviations: AE, adverse event; *ADRA*, adrenoceptor alpha; *ADRB*, adrenoceptor beta; AKI, acute kidney injury; CL, clearance; C_{max}, maximum serum concentration; CPG, clinical practice guideline; Cp, plasma concentration; CVICU, cardiovascular intensive care unit; CYP, cytochrome p450; FDA, Food and Drug Administration; *GABRA*, gamma-aminobutyric acid receptor alpha; *GABRB*, gamma-aminobutyric acid receptor beta; HIE, hypoxic ischemic encephalopathy; ICU, intensive care unit; INR, international normalized ratio; JET, junctional ectopic tachycardia; NICU, neonatal intensive care unit; PBPK, physiologically based pharmacokinetic; PD, pharmacodynamics; PGx, pharmacogenomics; PICU, pediatric intensive care unit; PK, pharmacokinetics; PopPK, population pharmacokinetics; rs, reference single-nucleotide polymorphism cluster ID; SNP, single-nucleotide polymorphism; TCI, target-controlled infusion; UGT, uridine 5_0-diphospho-glucuronosyltransferase; Vd, volume of distribution.

Study Highlights

WHAT IS THE KNOWLEDGE ON THE TOPIC?

Dexmedetomidine is commonly used off-label for continuous and procedural sedation in pediatrics. It is a popular choice because of its safety profile, but it has variable response within adult and pediatric populations.

WHAT QUESTION DID THIS STUDY ADDRESS?

What is the most current knowledge of dexmedetomidine PK, PD, and PGx in pediatrics, and what are the identified causes of variability?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

Dexmedetomidine PK depends on body size and age, with younger children potentially requiring a wider dosing range. While genotype impacts dexmedetomidine metabolism, current evidence does not support genotype-guided dosing. Data are mixed regarding cardio/renal protection, but shows promise for sedation, shivering prevention, and opioid reduction in neonates with HIE.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

This review summarizes the impact of PK, PGx, clinical status, age, and size on dexmedetomidine's behavior in children. This can guide providers in identifying covariates that will impact their patients' PK/PD. Additionally, we summarize recent PGx findings regarding SNPs, which may guide future pediatric pharmacogenomic research on dexmedetomidine.

INTRODUCTION

Children admitted to the pediatric intensive care unit (PICU) are frequently sedated with medications including opioids, benzodiazepines, and the alpha-2-adrenergic receptor agonist, dexmedetomidine.[1] Extensive dose titration and multiple drugs are often required to achieve sedation.[2,3] Dexmedetomidine has become a mainstay of sedation in critically ill children due to increasing evidence of impaired cognition and adverse events (AEs) associated with benzodiazepine use in young children, combined with dexmedetomidine's generic availability and affordability.[4,5] The 2022 Society of Critical Care Medicine Practice Guidelines recommend using dexmedetomidine as a first-line agent for sedation in pediatric postoperative patients with expected early extubation.[5] However, there is an evidence gap for accurate pediatric dosing of dexmedetomidine, in part due to the pharmacokinetic variability in pediatric patients.

The Food and Drug Administration (FDA) labeling for dexmedetomidine states that it should be used for less than 24 h in adult patients for procedural sedation or for continuous infusion in the intensive care unit (ICU).[6] In pediatrics, it is indicated for short-term sedation during noninvasive procedures, such as an MRI. However, the FDA determined that safety and efficacy end points have not been met for procedural or continuous sedation in pediatric patients.[6–9] The end points for procedural sedation included adequate sedation at least 80% of the time, no use of rescue sedation, and no artificial ventilation or hemodynamic intervention.[8] The end point for continuous sedation was a significant difference in rescue sedation demand between the two stratified dexmedetomidine dose groups. Per the FDA's clinical pharmacology review, the safety end points of these studies were not adequately quantified or objectively measured, which led to inconclusive safety findings.[7–10]

Despite limited FDA labeling, dexmedetomidine is widely used for sedation during invasive procedures and long-term sedation in pediatric clinical settings, including the PICU, neonatal ICU (NICU), and cardiovascular ICU (CVICU).[1] Dexmedetomidine is a sedative of particular interest in children because of its ability to mimic natural sleep and possibly reduce analgesic medication load.[13] However, continuous infusions of dexmedetomidine can vary widely from doses of 0.2–1.5 μg/kg/h.[11,12] Dose titration is not standardized and can take up to several hours before achieving an appropriate comfort goal, leaving patients at risk for over or undersedation.[5,10] Information on dose or covariate-related sedation, pain reduction, and AE occurrence is crucial for therapeutic optimization of dexmedetomidine.

The interplay between pharmacodynamics (PD), pharmacokinetics (PK), and pharmacogenomics (PGx) of dexmedetomidine is important to investigate and summarize, as the dose required to achieve optimal sedation

can vary widely from patient to patient.[11,14,15] According to the FDA, the weight-based volume of distribution and clearance are relatively consistent in all ages, ranging from 0.8–1 L/kg and 0.9–1.2 L/kg/h, respectively, in patients 1 month old up to 17 years old.[16] Adults have shown larger volumes of distribution, ranging from 1 to 2 L/kg, and consistent clearance at ~0.5 L/kg/h.[9,16] Inter-individual variability in PGx and dexmedetomidine metabolism can lead to PK and potentially PD alterations. Polymorphic variability can occur in dexmedetomidine's metabolic pathway through uridine 5_0-diphospho-glucu ronosyltransferase (UGT) and Cytochrome p450 (CYP) enzymes. Based on in vitro studies from literature and studies conducted in-house by our group, dexmedetomidine's hepatic metabolism is primarily (70%–95%) mediated via *UGT2B10*,[17–19] with small contributions from *UGT1A4* (~5%), and *CYP* enzymes (~3%–20%), including *CYP2D6 CYP3A4*, *CYP2A6*, *CYP1A2*, *CYP2E1*, *CYP2C19*, *and CYP2C9*.[8] As some hepatic enzymes can develop after birth, causing reduced clearance in certain age groups,[11] age-dependent maturation could play a role in pediatric PK variability with dexmedetomidine. Its site of action, adrenoceptor alpha 2A (*ADRA2A*), can also be a source of polymorphic variability, with eight variants reported in literature,[20–24] PGx variability of both metabolic and adrenergic pathways can alter dexmedetomidine's PK and/or PD.

PK and PD data can be combined through models to assess the effect of covariates, such as PGx, body weight, and age on clearance (CL), the volume of distribution (Vd), and efficacy, for example, sedation scores or AEs, for example, delirium scores, blood pressure, and heart rate. In this review, we will summarize data from PK, PD, and PGx studies of dexmedetomidine in pediatric patients (ages 0–18), and dexmedetomidine-related pharmacogenes in both adult and pediatric patients.

METHODS

This systematic review was carried out using PubMed and Ovid. The search terms used were 'dexmedetomidine' AND ('pharmacokinetics' OR 'pharmacodynamics' OR 'pharmacogenetics' OR 'pharmacogenomics'). Additionally, we reviewed the reference lists of all identified studies and reviews. The last search using these terms was conducted in May 2024. A thorough review on dexmedetomidine PK and PD was published in 2017 by Weerink et al.,[11] therefore, we decided to only include PK and PD studies published after 2017. As there are fewer PGx data available for dexmedetomidine as compared with PK and PD data, we included published PGx studies dating back to 2011. We included controlled trials, cohort studies, PopPK models, physiologically-based pharmacokinetic (PBPK) models, and case–control studies which included pediatric patients. We excluded case reports, meta-analyses, conference abstracts, and review papers, as well as non-english papers. We identified 26 studies that met the inclusion criteria and are evaluated in this review. Two reviewers collected and verified data from each report.

RESULTS

Allometric scaling and ontogeny

Dexmedetomidine is dosed based on weight (μg/kg/h), but in young pediatric patients (<3 years old) it exhibits variable PK, indicating that other covariates, such as age and organ maturation (ontogeny) may play a role in variability of drug response. Eight population pharmacokinetic (PopPK) studies have evaluated dexmedetomidine PK using weight as a covariate, either by incorporating data from both children and adults or using allometric scaling, which uses an average adult weight of 70 kg as a scaling factor for all PK parameters (Table 1).[11,14,15,25] We identified three studies which provide analyses of adult and pediatric data.[14,15,25] Morse al. describe a shortcoming of target-controlled infusion (TCI) pumps, which are programmed to infuse medication to a target plasma concentration (Cp).[15] Anesthesiologists use patient parameters, such as sex, weight, age, etc. to program this automated infusion and target a predefined Cp.[27] A limitation of TCIs is that their programming is based upon adult data only, but TCI pumps are often used in pediatric patients. The goal of Morse's model was to provide a universal scaling factor to better predict pediatric PK of dexmedetomidine, improving targeted dosing for both children and adults.[15] For this, they used PK data from five previously published studies[27–31] to estimate the pharmacokinetic outcomes of TCI in a pediatric model (Table 1). They found a direct relationship between age and CL in the first few years of life, and an inverse relationship between patient size and CL after the age of 3, likely due to an age-related plateau in organ maturation. The authors used their model to provide a guide incorporating both age and size as scaling factors for patient dosing.[15] Based on this guide, a theoretical neonate with an estimated weight of 3.6 kg would require doses of ~0.77 μg/kg/h to maintain a target plasma concentration of 1 ng/mL (a target concentration which produces moderate to deep sedation in most infants and children).[25,32,33] This requirement increases with age, peaking at ~1.04 μg/kg/h by 3 years old, based on a predicted age-dependent (or ontogenic) increase in metabolic clearance.[15] Disma

TABLE 1 Allometric scaling.

References	Study type	Population	Dose; duration	Methods	Results	Conclusions
Ber[14]	PopPK model	Setting: ICU Age: 3 months-88 years *N* = 70 patients	Continuous infusion: 0.08–2 μg/kg/h	Model: 2-compartment Covariates: Age, weight demographics, PGx, study type, hemodynamics, and sedation scores	V1: 22.5 L V2: 86.1 L Vss: 108.6 L CL: 34.7 L/h Q2: 40.8 L/h Significant covariates: Age, body weight, CYP1A2*1F genotype and noradrenaline use	Predicted CL was slightly low (33.7–53.4 L/h) Other model parameters aligned with literature values
Damian[34]	PopPK Model	Setting: ICU Population: Liver transplant recipients Age: 1 month-18 years *N* = 20 children	Bolus: 0.5 μg/kg Infusion: 0.5 μg/kg/h	Model: 2-compartment Covariates: Ischemia, donor age, liver type, INR, tBILIi, and ALT	V1: 186 L/70 kg V2: 203 L/70 kg CL: 52 L/h Q2: 246 L/h Significant covariates: INR (for CL), weight (for Vd)	Weight was linearly correlated with V1, but CL was inversely correlated with INR Weight-based dosing may not correlate with CL, and titration to clinical effect or INR may be a more effective covariate
Disma[25]	PopPK Model	Setting: 5 pooled studies Combined Age: 0–60 years *N* = 167 1. Szmuk et al.[65] Age: 5.2–15.5 months *N* = 32 children 2. Potts et al.[28] Age: 1 week- 14 years *N* = 95 children 3. Cortínez et al.[29] Age: 20–60 years *N* = 20 patients 4. Rolle et al.[30] Age: 18–60 years *N* = 40 patients 5. Talke et al.[31] Age: 21–36 years *N* = 10 patients	Bolus: 1 μg/kg Infusion: 1 μg/kg/h	Model: 3-compartment Covariates: Age, and size	V1: 19 L/70 kg V2: 24.1 L/70 kg V3: 50 L/70 kg CL: 40 L/h/70 kg Q2: 82.2 L/h/70 kg Q3: 31 L/h/70 kg Significant covariates: Age, size	Cp was predictable using known covariates such as age and size

TABLE 1 (Continued)

References	Study type	Population	Dose; duration	Methods	Results	Conclusions
Greenberg[35]	PopPK Model	Setting: ICU Age: 33–61 weeks PMA *N* = 20 infants	Infusion: 0.5–2.5 μg/kg/h	Model: 1-compartment Covariates: Age, size, cardiac surgery, sex, Scr	Vdss: 1.5 L/kg CL: 0.87–2.65 L/kg/h Cp: 0.68 ng/mL Significant covariates: Age	When standardized to a 70-kg adult, the plasma CL of 48.2 L/h was lower than typical adult values CL increased by 4.5% per 1-week increase in PMA Recent cardiac surgery reduced CL by 40% Younger PMA and recent cardiac surgery may reduce overall DEX demand
James[36]	PopPK Model	Setting: Surgical and ICU Age: 0–22 years *N* = 354 patients	Bolus: 0.06–4.21 μg/kg Infusion: 0.03–2 μg/kg/h	Model: 2-compartment Covariates: Age, size sex, mortality score, length of ICU stay, CPB, Scr, allometry and PGx	V1: 161 L/70 kg V2: 7903 L/70 kg CL: 27.3 L/h/70 kg Q2: 26 L/h/70 kg Significant covariates: PMA and body weight	Both weight and age, but not genotype, had a significant impact on CL and Cp Allometric Scaling: In a 9.4 kg, 104.6-week-old child (PMA), the following parameters would be estimated: V1: 21.6 L V2: 1061.26 L CL: 6.04 L/h Q2: 5.7 L/h
Kim[37]	PopPK model	Setting: Surgical Age: 20.3 ± 19.3 months *N* = 29 children	Bolus: 1 μg/kg Infusion: 0.5 μg/kg/h during surgery Second Bolus: 1 μg/kg at initiation of CPB	Model: 2 and 3-compartment Covariates: Size, weight, age, fat-free mass, CPB and temperature	V1: 31.6 L V2: 90.1 L CL: 1.08 L/min/70 kg Q2: 2.0 L/min/70 kg V3: (associated with CPB) 39.4 L Significant covariates: 2897[a]	CPB termination significantly increased Cp (0.378 ng/mL vs. 0.266 ng/mL) which is explained by the removal of the third compartment created by bypass

(Continues)

TABLE 1 (Continued)

References	Study type	Population	Dose; duration	Methods	Results	Conclusions
Morse[15]	PopPK model	Setting: 5 pooled studies Combined Age: 0–72 years *N* = 153 1. Hannivoort et al.[27] Age: 20–70 years *N* = 18 healthy patients 2. Potts et al.[28] Age: 1 week- 14 years *N* = 95 surgical children 3. Cortínez et al.[29] Age: 20–60 years *N* = 20 surgical patients 4. Rolle et al.[30] Age: 18–60 years *N* = 40 surgical patients 5. Talke et al.[31] Age: 21–36 years *N* = 10 healthy patients	Study 1: TCI Study 2: 1–4 μg/kg bolus Study 3: 0.5 μg/kg bolus, then 0.25 or 0.5 μg/kg/h infusion Study 4: 0.5 μg/kg bolus, then 0.5 μg/kg/h infusion	Model: 3-compartment Covariates: Age, weight, free fat mass scaling	V1: 25.2 L/70 kg V2: 34.4 L/70 kg V3: 65.4 L/70 kg CL: 0.9 L/70 kg/min Q2: 1.68 L/70 kg/min Q3: 0.62 L/min/70 kg Significant covariates: Age, body weight	Size and age were significant covariates in the model CL increased with age; neonatal CL was 42% of adult levels, and CL in 3-year-olds was 80% Obesity was correlated with higher CL and Cp; 3.2 ng/mL vs. 2.6 ng/mL
Song[38]	PopPK Model	Setting: ICU Age: 3–10 years *N* = 29 children	Low dose group Bolus: 0.25 μg/kg Infusion 0.25 μg/kg/h for 50 min High dose group Bolus: 0.5 μg/kg Infusion: 0.5 μg/kg/h for 50 min	Model: 2-compartment Covariates: Age, size height, weight, and body fat	V1: 64.2 L/70 kg V2: 167 L/70 kg CL: 81.0 L/70 kg/h Q2: 116.4 L/70 kg/h Significant covariates: Body weight	Both groups showed increased CL and Vd Both groups attained moderate-deep sedation, despite different doses AEs were not correlated with dose

Abbreviations: AE, adverse event; AKI, acute kidney injury; ALT, alanine transaminase; CL, clearance; CPB, cardiopulmonary bypass; CP, plasma concentration; DEX; dexmedetomidine; ICU, intensive care unit; INR, international normalized ratio; PGx, pharmacogenomics; PMA, postmenstrual age; PopPK, population pharmacokinetics; PK, pharmacokinetics; Q, distribution rate; Scr, serum creatinine; tBILI, total bilirubin; TCI, target-controlled infusion; V, Vd, volume of distribution; Vdss, volume of distribution at steady state.

[a]CPB correlation with PK was significant, but model was rejected due to inconsistencies in parameter estimations and model predictions.

et al. pooled the adult literature data from Morse's model with their primary data collected from pediatrics to validate the use of the universal model, and found that both models had consistent PK predictions.[15,25] In their study, age was the primary covariate for PK in patients under 2 years of age, and weight was the primary covariate in patients 2 and over.[25]

Independently, Ber et al.[14] developed a PopPK model incorporating allometric scaling and ontogeny. This model included a wide variety of doses in adult and pediatric patients, starting at 0.7 μg/kg/h in adults and 0.8 μg/kg in pediatrics without a loading dose, continuing at 0.08–2 μg/kg/h. In contrast to Morse's PK model, which investigated size, age, and fat-free mass as covariates, Ber included 26 additional covariates including PGx, hemodynamics, and sedation scores (Table 1).[14] In addition to the significant covariates of age and body weight, authors found that noradrenaline administration significantly reduced clearance (theoretically by constricting hepatic blood flow), and *CYP1A2*1F* (rs762551) allele was associated with increased dexmedetomidine clearance (Tables 3 and 4).[14] Due to the high amount of covariates assessed in a relatively small sample size, application in clinical practice may be less useful than models with larger sample sizes and/or less covariates included in the model.

Five PK studies using exclusively pediatric data have included allometric scaling in their analysis and discussion (Table 1).[34–38] Separately, three of these studies noted direct effects of weight via allometric scaling on Cp and CL.[34–36] One study by Damian et al.[34] noted a linear correlation between weight and Vd. These results align with the above data from adult and pediatric studies: Body size is significantly correlated with the kinetics of dexmedetomidine. Morse et al.[15] estimated that 83% of between-subject variability in their simulated pediatric patients was due to allometry, which can be controlled by accounting for weight. James et al.[36] affirmed this conclusion, showing that age plays less of a role as patients get older, and that weight is the primary significant covariate for clearance in patients over 93 weeks postmenstrual age. Body size in patients over the age of ≥3, and ontogeny in patients <3, should be the primary considerations for providers when initiating dexmedetomidine in a pediatric patient.

Pharmacokinetics/pharmacodynamics

Multiple studies have investigated the relationship between dose, kinetics, and sedation scores. We identified 10 studies in exclusively pediatric patients that provided new, relevant information on the PK and PD of dexmedetomidine (Table 2).[32,33,39–46] These studies used plasma sampling, vital signs and laboratory data collection, and PK modeling to assess dexmedetomidine distribution, metabolism, elimination, and clinical effects in children. PD outcomes of interest include sedation and responsiveness – which are direct measures of drug efficacy – as well as safety outcomes, such as bradycardia, hypotension, and delirium.

I. Procedural sedation

Physiologic changes during and after surgery may play a role in the PK of dexmedetomidine. As demonstrated in Kim et al.'s[37] procedural study and PopPK model, dexmedetomidine distribution into a third compartment is enhanced when patients undergo cardiopulmonary bypass. This dispersion within the body leads to a significant decrease in dexmedetomidine Cp during bypass, $p < 0.016$ (Table 2).[37] Both Morse et al. and Disma et al.[15,25] found that a 3-compartment PopPK model best fit their data in patients undergoing procedural anesthesia for ≥2 h. This third spacing may occur during surgical procedures due to blood flow alterations and increased capillary wall permeability, temporarily reducing the availability of drug in the plasma. This can result in increased sedative demand due to reduced dexmedetomidine concentration at the target site. Such elevated sedation demand was seen in practice in the PK analysis of the interventional arm of Disma et al.'s[25] study, but target sedation was obtained by increasing target plasma concentrations from 0.6 to 1 ng/mL (Table 1).

When used for procedural sedation, dexmedetomidine may also reduce demand for other sedative and analgesic medications.[5,11,39] Amula et al.[39] documented a statistically significant reduction in overall intraoperative benzodiazepine and opioid load for patients (Table 2). Of note, patients were exposed to significantly higher doses (12.5 vs. 5.8 μg/kg, $p = 0.04$) of dexmedetomidine, and nonsignificantly higher doses of propofol and acetaminophen, but authors did not document AEs as a result of these exposures. Patients were also not exposed to higher doses of volatile anesthetic.[39] Combined with the above study results, these data indicate that short-term exposure to dexmedetomidine during surgery, when administered at high enough doses, may be a protective factor against the need for opioids and other sedating medications.

IA. Adverse events in procedural sedation

Dexmedetomidine PK and PD effects on target organs, including the kidney, heart, and liver, have been reported in surgical pediatric patients. Jo et al.[43] investigated the correlation between dexmedetomidine and postoperative acute kidney injury (AKI). AKI is defined as an absolute

TABLE 2 Pediatric PKPD studies.

	Study type	Population	Dose; Duration	Methods	Results	Conclusions
Amula[39]	Multicenter retrospective analysis of CPG implementation	Setting: Surgical Age: 14 days- 6 months $N = 240$ children	Infusion: 1 μg/kg, titrated up	Analysis of total intraoperative opioid, benzodiazepine, and volatile anesthetic exposure	Median opioid dose was reduced from 49.7 to 24 μg/kg of fentanyl equivalents ($p < 0.001$) Median benzodiazepine dose reduced from 1 to 0.4 mg/kg of midazolam equivalents ($p < 0.001$) Procedural DEX was associated with early extubation Use of acetaminophen and propofol increased nonsignificantly	CPG implementation led to more patients receiving DEX, but at a lower dose Increased use of DEX led to lower opioid and benzodiazepine exposure without need for more volatile anesthetic
Dersch-Mills[40]	Retrospective chart review of term and preterm neonates receiving continuous DEX	Setting: ICU Age: 23–40 weeks GA $N = 38$ neonates	Infusion: 0.2–0.3 μg/kg/h, titrated up	Analysis of DEX effect on concomitant sedative/analgesic/clonidine doses, as well as AEs Comparison of weight-based dose effects	−66.7% of patients had opioids reduced within 24 h of starting dexmedetomidine ($p = 0.798$) 88.9% experienced at least one AE Dose ≥0.5 μg/kg/h: 50% experienced hypotension, 27.3% experienced severe bradycardia Dose <0.5 μg/kg/h: 25% experienced hypotension, 7.7% experienced severe bradycardia	DEX did not significantly reduce opioid dosing Patients on max doses of 0.5 μg/kg/hour or higher should be closely monitored for AEs
Elliott[41]	Dual-center retrospective analysis of Quality-improvement initiative	Setting: ICU Age: 37–39 weeks GA $N = 135$ neonates with HIE	Infusion: 0.3 μg/kg/h, titrated up	Initiative using DEX as a first-line therapy for sedation during therapeutic hypothermia Retrospective analysis of opioid exposure reduction and patient outcomes with the initiative	Mean cumulative fentanyl exposure was reduced from 30 to 1.7 mcg/kg Mean cumulative morphine exposure was reduced from 648 mcg/kg to 85 mcg/kg	DEX is effective as a first-line agent for sedation in HIE patients Use of DEX as a first-line agent in this population leads to opioid exposure reductions of ≥87%

TABLE 1 (Continued)

	Study type	Population	Dose; Duration	Methods	Results	Conclusions
Hassan[42]	Randomized controlled trial on cardiac protection of DEX in young children	Setting: Surgical Age: 4 months-5 years $N = 120$ children	Group MD Bolus: DEX 0.5 μg/kg + $MgSO_4$ 50 mg/kg Infusion: DEX 0.5 μg/kg/h + $MgSO_4$ 30 mg/kg/h × 72 h postoperative Group D Bolus: DEX 0.5 μg/kg + NS Infusion: DEX 0.5 μg/kg/h + NS × 72 h postoperative Group C Bolus: NS Infusion: NS × 72 h postoperative	Comparison of junctional ectopic tachycardia (JET) occurrence after cardiac surgery with DEX and $MgSO_4$ vs. DEX alone vs. control (NS)	JET risk was significantly reduced with DEX ± $MGSO_4$ ($p = 0.032$), OR: 0.26 for DEX and $p = 0.008$, OR: 0.06 for DEX + $MgSO_4$ Extubation time, duration of cardiac care unit stay and total length of hospital stay were significantly reduced with DEX ± $MGSO_4$	Use of dexmedetomidine with or without $MgSO_4$ improves cardiac safety outcomes following cardiac surgery, and reduces length of post-surgical hospital stay
Jo[43]	Randomized, prospective, placebo-controlled study	Setting: Surgical Age: 1–6 years $N = 29$ children	Bolus: 0.5 μg/kg Infusion: 0.5 μg/kg/h Or Placebo	Analysis of AKI occurrence in patients receiving DEX vs. placebo	AKI incidence was significantly higher in the control group (64% vs. 27%, $p = 0.042$) eGFR was significantly lower in the control group than the DEX group (72.6 ± 15.1 vs. 83.9 ± 13.5, $p = 0.044$)	Perioperative DEX reduced the risk of AKI in pediatric cardiac surgery patients
Kim[44]	Randomized, prospective, placebo-controlled study	Setting: Surgical Age: 1.5–2 years $N = 139$ children	Bolus: 1 μg/kg Infusion: 0.5 μg/kg/h Post-CBP Bolus: 1 μg/kg Or Placebo	Analysis of AKI occurrence in patients receiving DEX vs. placebo	AKI incidence was not different between groups (17% in DEX and vs. 24%) eGFR was significantly lower and creatinine was higher in the control group than DEX ($p = 0.02$)	Intraoperative DEX reduced the risk of AKI in pediatric cardiac surgery patients
Lin[45]	Prospective, observational single center study	Setting: ICU Age: 0–16 years $N = 1134$ children	Not reported	Development of a delirium risk prediction model based on data from after major surgery Analysis of benzodiazepine, propofol, corticosteroid, anticholinergic, opioid, paralytic and DEX use, pain and sedation scores	11.1% of patients were diagnosed with delirium, in a median of (40 min) after surgery 67.5% of patients who developed delirium received DEX, vs. 57.2% who did not develop delirium	Single predictive factors had less predictive probability than the predictive model, indicating that when DEX is combined with other risk factors, the patient is at increased risk of delirium

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TABLE 1 (Continued)

	Study type	Population	Dose; Duration	Methods	Results	Conclusions
Mcadams[32]	PopPK Model	Setting: ICU Population: Neonates with HIE Age: 37–41 weeks GA $N = 7$ neonates	Infusion: 0.2 μg/kg/1 h, then 0.3 μg/kg/h for 2.5 h, then 0.4 μg/kg/h	Model: 1 compartment Covariates: Age, weight, ALT, Scr, cooling duration and body temperature fluctuations	Vd: 7.48 L/kg CL: 0.697 L/kg/h Cp: 0.300–0.900 ng/mL Significant covariates: None	CL was low, but Vd, MRT, and $t_{1/2}$ were higher compared with normothermic, non-HIE neonates In cooled neonates with HIE, a loading dose or more rapid titration may be needed DEX adequately controlled pain/sedation in 85% of the patients, and controlled shivering in 5 of 7 without rescue morphine
Takeuchi[46]	Clinical study on age-specific dexmedetomidine dosing in the PICU	Setting: ICU Age: 45 weeks CGA- 17 years old $N = 61$	<6 years old Infusion: 0.2–1.4 μg/kg/h ≥6 years old Infusion: 0.2–1.0 μg/kg/h	Analysis of DEX Cp and effect on 24-hour rescue midazolam or fentanyl demand, AEs and sedation scores	77% of patients did not require rescue midazolam 88.5% did not require rescue analgesic fentanyl	Age-specific dose regimens without a loading dose achieved adequate sedation without clinically significant AEs A goal Cp of 0.3–1.25 ng/mL may mitigate hemodynamic and respiratory AEs
van Dijkman[33]	PopPK Model	Setting: ICU Age: 34–44 weeks PMA $N = 6$	Infusion: 0.3 μg/kg/h	Model: 2 compartment model Covariates: PMA and weight	V1: 80.4 L V2: 142 L CL: 42.1 L/h Q2: 12.5 L/h −83% of patients needed fentanyl rescue Significant covariates: PMA	0.3 μg/kg/hour infusion over 24 h reached concentrations just below 0.6 ng/mL, with 95% of neonates under 1.0 ng/mL and 83% above 0.4 ng/mL CL for a typical neonate, PMA of 40 weeks, 3.4 kg, was 2.92 L/h Higher target Cp may be necessary for neonatal sedation

Abbreviations: AE, adverse event; ADRA2A, adrenoceptor alpha 2a; AKI, acute kidney injury; ALT, alanine transaminase; BP, blood pressure; CGA, corrected gestational age; Cl, clearance; CPB, cardiopulmonary bypass; CPG, clinical practice guideline; CP, plasma concentration; CYP, cytochrome p450; DAP, diastolic arterial pressure; DEX; dexmedetomidine; eGFR, estimated glomerular filtration rate; GA, gestational age; HIE, hypoxic ischemic encephalopathy; ICU, intensive care unit; IIV, inter-individual variability; INR, international normalized ratio; JET, junctional ectopic tachycardia; $MgSO_4$, magnesium sulfate; MRT, mean residence time; NS, normal saline; PD, pharmacodynamics; PMA, postmenstrual age; PopPK, population pharmacokinetics; PK, pharmacokinetics; PGx, pharmacogenomics; Q, distribution rate; rs, reference single-nucleotide polymorphism cluster ID; SAP, systolic arterial pressure; Scr, serum creatinine; SNP, single-nucleotide polymorphism; $t_{1/2}$, half-life; TCI, target-controlled infusion; UGT, uridine 50-diphospho-glucuronosyltransferases; UHPLC–MS/MS, ultra performance liquid chromatography – tandem mass spectrometer; V, Vd, volume of distribution.

TABLE 3 Adult and pediatric pharmacogenomic studies.

References	Study type	Population	Dose; duration	Genes studied	Results	Conclusions
Ber[14]	PopPK model	Setting: ICU Age: 0.25–88 years $N=70$	Continuous infusion: 0.08–2 μg/kg/h	CYP1A2, CYP2A6, CYP2A6, UGT2B10, CYP2E1, CYP2C19, CYP2D6	Inclusion of CYP1A2*F genotype and norepinephrine decreased IIV by ~5% (≥20% reduction is needed for clinical significance)	CYP1A2*1F (*rs762551*) genotype and norepinephrine were identified as statistically, but not clinically significant covariates for DEX CL
Choi[22]	Prospective trial	Setting: Surgical Age: ≥50 years $N=134$ patients	Infusion: 2 μg/kg	ADRA2A polymorphisms vs wild-type	No differences in total DEX doses or sedation scores	Genetic polymorphisms of ADRA2A did not appear to impact the efficacy of DEX
Ding[59]	Prospective trial	Setting: Surgical Age: 41.88 ± 14.40 $N=92$ patients	Bolus: 0.5 μg/kg for 10 min Infusion: 0.4 μg/kg/h	CYP2A6, UGT1A4, UGT2B10, ADRA2A, ABCG2, ABCB1, ABCC2, ABCC3, SLCO1B1, SLC22A1, CYP1A2, CYP2C19, CYP2D6, WBP2NL, SLC31A1, KATP, KCNJ11, KCNMB1, KCNMA1, KCNN4, CACNA1D, CACNA1C, ABCC9, ADRB2, COMT, GNB3, PRKCB, and PRKCH	ADRA2A rs1800544 C allele carriers required higher doses of dexmedetomidine to achieve sedation CYP2D6 rs16947 A allele carriers achieved sedation at lower doses Clinical response was significantly altered by transporters ABCG2, WBP2NL, KATP, KCNMB1, KCNMA1, ABCC9, ADRB2	Both ADRA2A and CYP2D6 polymorphisms impacted patient response to DEX, indicating that response variability is multifactorial Transporter SNPs appear to impact DEX response
Fang[56]	Prospective cohort study	Setting: Surgical Age: 18–60 years $N=194$ females	Infusion: 1 μg/kg for 10 min, followed by standard anesthesia	CYP2A6, UGT2B10, UGT1A4, ADRA2A, ADRA2B, ADRA2C, GABRA1, GABRA2, GLRA1	Carriers of the minor allele (C) of CYP2A6 rs28399433 had higher Cp and increased sedation scores The GG allele of GABRA2 rs279847 polymorphism was significantly associated with HR abnormality	CYP2A6 rs28399433 C allele likely has lower metabolic efficiency and/or better binding, increasing drug exposure and sedation
Fu[21]	Prospective clinical trial	Setting: Surgical Age: 20–36 years $N=434$ women	Bolus: 4 mg intrathecal, followed by 0.5 μg/kg IV	ADRA2A polymorphisms vs wild-type	Post-anesthesia, PTh and PTTh of wild-type birth-givers increased significantly more than those with SNPs containing G or T alleles	Mutations of rs1800035, rs201376588 and rs775887911 in ADRA2A appear to reduce the anesthetic and analgesic effect of DEX in adult women Wild-type ADRA2A likely has increased metabolic efficiency and/or better binding than polymorphic ADRA2A in this population

(Continues)

TABLE 3 (Continued)

References	Study type	Population	Dose; duration	Genes studied	Results	Conclusions
Gallaway[23]	Prospective observational study	Setting: ICU Age: 1 week- 18 years *N* = 40 children	Infusion: 0.22–1.3 μg/kg/h	ADRA2A polymorphism vs. wild-type	Patient age and time to effective dose, but not genotype, was significantly correlated with DEX mean dose	DEX PK and PD does not seem to differ between wild-type and variant ADRA2A rs1800544 genotypes
Guan 55	Application of UHPLC–MS/MS method	Setting: Surgical Age: 2–72 months *N* = 260 children	Intranasal: 3 μg/kg	CYP2A6 polymorphisms vs wild-type	CYP2A6 rs835309 T allele carriers were significantly correlated with lower Cp than wild-type (0.397 ng/mL vs. 0.456 ng/mL)	There may be a correlation between CYP2A6 rs835309 polymorphisms and DEX Cp in pediatric patients
James[36]	PopPK Model	Setting: Surgical and ICU Age: 0–22 years *N* = 354 children	Infusion: Median 0.6 μg/kg/hour over a median duration of 2 h	UGT1A4, UGT2B10, and CYP2A6 polymorphisms vs. wild-type	Genotype had no statistically significant impact on CL or Cp	Despite 20% estimated CL reduction with UGT1A4 variants, there does not appear to be a significant impact of UGT1A4, UGT2B10, or CYP2A6 genomic variation on pediatric DEX PK
Shannon[57]	GWAS and PopPK Model	Setting: Surgical and ICU Age: 5 months-6 years *N* = 280 children	Not reported	1,121,432 genetic variants Covariates: UGT1A4, UGT2B10, CYP2A6, age, PNA, PMA weight, sex, mortality score, CPB time, length of ICU stay, Scr	36% of the heritable variability was due to 2997 small-effect variants 26% heritable variability was due to 264 moderate-effect variants 38% heritable variability was due to 57 large-effect variants. Significant covariates: PMA and body weight	While high variability was demonstrated, no single polymorphism or gene was significantly associated with PK alterations DEX variability is highly polygenomic in nature
Yaar[20]	Prospective Trial	Setting: Surgical Age: 36–80 years *N* = 110 patients	Continuous Infusion: 1.4 μg/kg/h	ADRA2A polymorphisms vs. wild-type	Patients carrying variant G allele of ADRA2A 1291G (rs1800544) had decreased sedative response There were no genotypic differences in the hemodynamic (SAP, DAP, HR) responses, or in DEX dose	There appears to be a weak clinical effect of ADRA2A 1291G allele presence in response to DEX

TABLE 3 (Continued)

References	Study type	Population	Dose; duration	Genes studied	Results	Conclusions
Zhu[58]	Prospective trial	Setting: Surgical Age: 27 to 60 years $N = 60$ patients	Infusion: 1 μg/kg over 10 min	ADRA2A polymorphisms vs wild-type	ADRA2A rs1800544 C allele carriers had significantly lower HR than wild-type There was no significant BP or sedation score difference between the A1780G and C-1291G polymorphisms and wild-type	ADRA2A C-1291G polymorphism may affect HR changes in adult patients after DEX infusion Younger age (41 ± 7.51 years) was associated with higher HR reduction than older age (47.95 ± 7.19 years)

Abbreviations: AE, adverse event; ADRA2A, adrenoceptor alpha 2a; AKI, acute kidney injury; ALT, alanine transaminase; BP, blood pressure; CGA, corrected gestational age; Cl, clearance; CPB, cardiopulmonary bypass; CP, plasma concentration; CYP, cytochrome p450; DAP, diastolic arterial pressure; eGFR, estimated glomerular filtration rate; GA, gestational age; HIE, hypoxic ischemic encephalopathy; HR, heart rate; ICU, intensive care unit; IIV, inter-individual variability; INR, international normalized ratio; MRT, mean residence time; PD, pharmacodynamics; PMA, postmenstrual age; PopPK, population pharmacokinetics; PK, pharmacokinetics; PGx, pharmacogenomics; Q, distribution rate; rs, reference single-nucleotide polymorphism cluster ID; SAP, systolic arterial pressure; Scr, serum creatinine; SNP, single-nucleotide polymorphism; t1/2, half-life; tBILI, total bilirubin; TCI, target-controlled infusion; UGT, uridine 50-diphospho-glucuronosyltransferases; UHPLC–MS/MS, ultra performance liquid chromatography - tandem mass spectrometer; V, Vd, volume of distribution; Vss, volume of distribution at steady state.

increase in serum creatinine of either ≥0.3 mg/dL, or ≥50%, or a decrease in urine output of <0.5 mL/kg/h for >6 h.[47] Compared with a matched infusion of normal saline, dexmedetomidine significantly reduced the incidence of AKI and increased estimated glomerular filtration rate (eGFR) in a randomized controlled trial (Table 2).[43] There were no significant differences in pressor requirements or hemodynamics, and no diuretics were used during and after the surgery. Patients received equal doses of anesthesia and benzodiazepines.[43] The alpha-2-agonism and anti-inflammatory effects of dexmedetomidine may have a reno-protective effect in patients who are critically ill or undergoing surgery.[43,48,49] However, a randomized trial by Kim et al.[44] demonstrated that this effect may not be significant in a larger population ($n = 139$ vs. 29). In children receiving intraoperative dexmedetomidine vs. placebo, there was no significant difference in AKI or other clinical outcomes, although the dexmedetomidine group had lower overall serum creatinine and higher eGFR (within normal limits).[43,44] Notably, Kim's study group was younger in age than Jo et al.'s (1.5–2 vs. 1–6 years old) and received a higher loading dose (1 μg/kg vs. 0.5 μg/kg). While there is a numerical difference in the renal outcomes of these patients (Table 2), there is weak evidence of dexmedetomidine being clinically reno-protective during surgery.[43,44]

Due to its mechanism of action and metabolic pathway, dexmedetomidine may have noteworthy PK/PD interactions related to cardiac and hepatic function. A potential benefit of its alpha-2-agonism is the reduction of junctional ectopic tachycardia (JET) incidence, a life-threatening arrythmia that can occur after congenital heart surgery.[42] Kim et al.'s[44] study, as described above, found no difference in postoperative JET or other arrhythmia occurrence between the dexmedetomidine and placebo groups (Table 2). However, in a 2024 study, Hassan et al. compared JET occurrence in three groups of randomized pediatric cardiac surgery patients: Group MD, receiving IV dexmedetomidine and magnesium sulfate; Group D, receiving dexmedetomidine alone; and Group C (control). JET occurred in 30% of the control group vs. 10% of group D and 2.5% of the group MD ($p = 0.007$). Use of dexmedetomidine alone or with magnesium significantly mitigated the risk of JET, shortening both cardiac care unit and hospital stays (Table 2).[42] Lastly, Damian et al. studied the PK of dexmedetomidine in patients between 1 month and 18 years of age after liver transplantation and determined that post-translation international normalized ratio (INR) was a covariate for clearance.[34] There was not an association between patient weight, distribution kinetics, liver transplant type (whole or split) donor, and dexmedetomidine CL (Table 2). The authors mentioned that this

TABLE 4 Pharmacogenomic alleles and effects.

Receptor polymorphisms											
			Clinical effects								
Enzyme	Rs number	Allele substitution (substitution frequency)	PT	PTTh	Pain markers (VAS, cortisol and blood glucose)	Sedation	Time to achieve sedation	Sedation demand	BP	HR	DEX demand/ dosing
ADRA2A	*rs1800035*[21]	*C > G (27%)*	↓	↓	↑	↓	[a]				
	rs201376588[21]	*C>T (30%)*	↓	↓	↑	↓					
	rs775887911[21]	*C>T (29%)*	↓	↓	↑	↓					
	rs1800544[20–23,56,58,59]	*G>C (30%)*				↓/=	=	=	=	↑/=	↑/=
	rs2484516[22,56]	*C>G (10%)*				=	=			=	=
	rs1800545[22]	*G>A (17%)*				=	=				=
	rs553668[22,56,58]	*G>A (16%)*				=	=		=	=	=
	rs3750625[22]	*A>G (53%)*				=	=				=
ADRA2B	*rs4907299*[56]	*G>T (53%)*						=		=	
	rs2229169[56]	*G>T (46%)*									
ADRB2	*rs1042713*[21]	*A>G (42%)*					↑				
ADRA2C	*rs11269124*[56]	*G>DEL (67%)*						=		=	
GABRA1	*rs77445936*[56]	*T>C (20%)*						=			
rs11576001[56]	*A>G (53%)*							=		=	
GABRA2	*rs279847*[56]	*G > T (75%)*						=		=	
	rs10433685[56]	*G>C (31%)*						=			
GABRB2	*rs10214094*[56]	*A>G (8%)*						=	=		

Metabolic polymorphisms									
			Clinical effects						
Enzyme	Rs number	Allele substitution (substitution frequency)	HR	BP	DEX demand/ dosing	Sedation	Cp	CL	Vd
CYP1A2	*rs762551*[14,59]	*A>C (40%)*	=	=		=			
CYP2A6	*rs113288603*[56]	*C>T (48%)*						=	
	rs56113850[56,59]	*T>C (32%)*	=	=		=		=	
	rs835309[36,55]	*G>T (16%)*					↓	=	
	rs2839y94[14,36,56,59]	*A>C (29%)*	=	=		↑	↑	↓/=	↓/=
	rs143731390[14,59]	*T>A (11%)*	=	=		=	=	=	=

TABLE 4 (Continued)

Metabolic polymorphisms									
			Clinical effects						
Enzyme	Rs number	Allele substitution (substitution frequency)	HR	BP	DEX demand/ dosing	Sedation	Cp	CL	Vd
CYP2C19	*rs4244285*[14,59]	*G>A (33%)*	=	=		=			=
	rs12248560[14,59]	*C>T (1%)*	=	=		=		=	=
CYP2D6	*rs1065852*[14,59]	*C>T (38%)*	=	=		=			
	rs28371725[14,59]	*A>G (4%)*	=	=		=		=	
	rs16947[14,21,59]	*G>A (15%)*	=	=	↓	↑		=	=
	rs3892097[14,59]	*G>A (1%)*	=	=		=		=	
	rs1135840[14]	*G>A (25%)*						=	=
UGT1A4	*rs6755571*[36]	*C > A (4%)*						=	
	rs3892221[36]	*C>T (1%)*							=
	rs2011425[36,59]	*A>C (21%)*	=	=		=		=	
	rs12468356[14,56]	*A>G (17%)*	=			=	=		=
	rs8330[14,56]	*C>G (10%)*	=			=	=		=
UGT2B10	*rs61750900*[9]	*G>T (7%)*						=	
	rs112561475[36]	*A>G (2%)*							=
	rs2942857[36]	*A>C (12%)*						=	=
	rs115455627[14,56]	*C>T (22%)*	=			=	=		=
	rs11940320[14,56]	*G>A (17%)*	=			=	=		=
	rs835309[59]	*G>T (49%)*	=	=		=			

Abbreviations: BP, blood pressure; Cp, plasma concentration; CL, clearance; DEX, dexmedetomidine; HR, heart rate; PT, pain 849 tolerance; PTTh; pain tolerance threshold; rs, reference single-nucleotide polymorphism cluster ID; VAS, visual analogue score; VD, volume of distribution; ↑ increase; ↓, decrease; =, no change.

[a]Cells left blank were not evaluated [] Reference allele for tri-allelic polymorphisms.

could be due to differences in transplanted liver mass-to-body weight (children often receive grafts which are bigger than their original organ).[34] While liver mass and dexmedetomidine clearance was not correlated with liver mass, tBILI or ALT in this study, INR proved to be a significant covariate for clearance (Table 1).[34] Dexmedetomidine is hepatically metabolized, and liver transplant patients are a unique case where weight may be a poor indicator of dose kinetics and response.[10,11,34] The results of these studies provide consistent but weak evidence of reno-protection and mixed evidence of arrhythmia reduction from perioperative dexmedetomidine. Damian et al.'s study also provides evidence that patients undergoing liver transplant should not be dosed exclusively based on body weight due to fluctuations in the function of the adapting liver.

II. Continuous sedation

The PK of dexmedetomidine differs when used for continuous sedation instead of procedural sedation. The concentration shift of dexmedetomidine into a third compartment may still occur, as many critically ill patients can experience dramatic fluid shifts and hypotension.[1,5,37] However, in contrast to the data from procedural sedation, most models for continuous sedation in the ICU found that a two-compartment model provided the most accurate data fit (Tables 1 and 2).[14,33,34,38] The relationship between dexmedetomidine distribution and clinical effect or AEs is not well documented. However, it is clear that both age and body size impact dexmedetomidine metabolism and demand.

In contrast to data on procedural opioid-sparing effects, continuous infusions of dexmedetomidine may not decrease the overall analgesic demand in the ICU. There have been several documented protocol implementations, in which investigators have made dexmedetomidine the first tool for patient comfort while allowing opioids to be used as a secondary therapeutic. Dexmedetomidine and opioids are titrated to a target effect (shivering, pain, or sedation level), in patients. The implementation of a dexmedetomidine clinical practice guideline did not significantly reduce opioid exposure in the NICU.[40] In their recently published study, and a follow-up chart review, Dersch-Mills et al. showed a clinical reduction in total opioid exposure and duration of opioid use but failed to demonstrate statistical significance (Table 2).[40,50] Authors argue that dexmedetomidine should not be given exclusively for opioid reduction in the NICU. In a study conducted by McAdams et al. on shivering prevention for neonates with hypoxic ischemic encephalopathy (HIE), it was found that dexmedetomidine could serve as a potential alternative to morphine, providing a non-opioid route for HIE care in the NICU (Table 2).[32] A larger study from Elliott et al.[41] in the HIE population demonstrated that dexmedetomidine can effectively and safely serve as a first-line alternative to morphine and other opioids for both sedation and shivering prevention. In this particular population, initiation of a protocol using dexmedetomidine as a first-line sedative led to decreased opioid exposures of 87%–95% (Table 2).[41] However, in the general neonatal ICU populations, there appears to be mixed evidence of opioid reduction with dexmedetomidine.[40,50] At the minimum, it seems to provide a clinical and numerical benefit in terms of overall patient comfort and analgesic burden.

In regards to sedation level, Song et al. found that during a short, continuous infusion of dexmedetomidine, there was no difference in sedation scores between patients randomized to high dose (0.5 μg/kg loading dose + 0.5 μg/kg/h) and low dose (0.25 μg/kg loading dose + 0.25 μg/kg/h) groups.[38] Patients in both groups attained the target of moderate to deep sedation, but it should be noted that these patients were recovering from immediate surgery where they had received a propofol TCI as well as sufentanil. This was the only study in our search which compared the effect of dexmedetomidine dose on sedation in the ICU.[38] Van Dijkman et al. did not compare sedation scores among doses but found that five of six neonates receiving 0.3 μg/kg/h of dexmedetomidine for 24 h needed rescue fentanyl for pain/sedation. While this is a small sample size, it suggests that in an extended duration of continuous sedation, higher doses may be needed to maintain target comfort and sedation scores.[33]

IIA. Adverse events in continuous sedation

When used in continuous sedation, dexmedetomidine may induce bradycardia and hypotension due to its alpha-2 agonism and has been independently associated with delirium risk.[13,40,41,51] According to the package insert, bradycardia occurs in up to 42% of adults and 57% of children, hypotension occurs in up to 56% of adults and 31% of children, and delirium has been documented at unspecified occurrence rates.[10] Dersch-Mills et al.'s study reported that 50% of patients on high dose (≥0.5 μg/kg/h) dexmedetomidine experienced hypotension and 27.3% experienced severe bradycardia, with only 25% and 7.7% of patients on low dose (<0.5 μg/kg/h) experiencing the same effects, respectively (Table 2).[40] These results were from a small sample, and were not statistically significant. In Elliott et al.'s study, 9.6% of neonates receiving ≤0.4 μg/kg/h discontinued dexmedetomidine due to bradycardia.[41] While no patients in

this study received ≥0.5 μg/kg/h (Table 2), this percentage aligns with data from Dersch-Mill et al., as well as previous studies and literature reviews.[40,52] Takeuchi et al. reported that 4.9% of children and infants experienced dexmedetomidine-related hypotension, and 11% experienced dexmedetomidine-related bradycardia, with no correlation to plasma concentration or dose.[46] Song et al's[38] group also noted no difference in bradycardia or hypotension between high and low doses of dexmedetomidine, although patients in this study only received an hour-long infusion.

Other pediatric studies have failed to show the correlation between dexmedetomidine concentration and adverse effects. A meta-analysis from Wang et al.[53] determined that there was no correlation between the clinical dose of dexmedetomidine and pediatric AEs, including bradycardia and hypotension. A model by Greenberg et al. showed no difference in critically ill infants between the average concentration of dexmedetomidine and the predicted concentration in moments of hypotension (0.42 ng/mL [0.28–0.56] vs 0.56 ng/mL [0.25–0.77], respectively; $p = 0.58$).[35] A confounding factor in these studies is the critical condition of the patients, which can cause hemodynamic alterations and changes in heart rate.[5,35,41,53] An interesting study conducted by Lin et al. showed that in critically ill patients, those who were receiving dexmedetomidine were at a higher risk for delirium than those who were not (Table 2).[45] This risk was considered additive with other factors, indicating that this adverse event occurs more frequently when patients have multiple risk factors, such as younger age, higher pain scores, or developmental delay.[45] Contrarily, Takeuchi et al.'s[46] group reported no delirium in 61 patients between 4 months and 6 years of age. Their demographic included young patients as well as high pain scores (91% receiving fentanyl for postoperative pain) but did not include patients with developmental delay.[46] Delirium with dexmedetomidine appears inconsistently in pediatrics, and may or may not be correlated with dexmedetomidine. The studies noted above show that dexmedetomidine's cardiovascular and vasoactive effects appear consistently in pediatrics, but do not appear to be dose-dependent during continuous sedation. The degree of hypotension and bradycardia may be dependent on genetic variability at the site of action, the *ADRA2A*, which is discussed in the next section.

Pharmacogenomics

PGx helps predict individual patients' response to target medications.[54] When considering genes relevant to dexmedetomidine response, there are two main areas of focus: (1) Variation in genes involved in metabolism and (2) variation in the adrenergic receptor, which is dexmedetomidine's site of action. Dexmedetomidine is extensively metabolized by direct N-glucuronidation by *UGT2B10 and 1A4* and, to a lesser degree, hydroxylation by *CYP* enzymes, including *CYP2A6* and*1A2*.[11,14,17–19]

PGx has been incorporated into PopPK models of dexmedetomidine. Ber et al. incorporated PGx, PD and PK data into their PopPK model (Table 3).[14] They found that the *CYP1A2*1F* (rs762551) allele presence was associated with ~1.5-fold higher clearance than wild-type (Table 4).[14] However, authors did not report associations between sedation scores and kinetics. The authors also noted that the identified covariates are of low clinical significance for dose adjustment, as they accounted for only ~5% overall variability. This variability may have been magnified by the heterogeneity of the studied population.[14] James et al. incorporated electronic health record data from a group of children under 2 years, post-cardiac surgery, into their PopPK model and estimated the pharmacokinetic effects of several genomic variants for *UGT1A4*, *UGT2B10*, *CYP2A6*.[36] In this large population, no genomic covariates were statistically significant (Table 4). *UGT1A4* variants of any kind were expected to have 20% reduction in clearance but did not appear to have a clinical effect according to the model.[36] Notably, their model did not incorporate the *CYP2A6* (rs835309), which was found to be a significant covariate in an earlier study of 260 pediatric surgical patients by Guan et al.[55] This study found that patients with this allele had significantly lower dexmedetomidine Cp than wild-type (Tables 3 and 4).[55] Further studies on this genomic mutation are needed to determine its clinical effect. Thus far, PopPK studies have not shown a correlation between metabolic genomic variants and clinical outcomes for dexmedetomidine. As noted above, *UGT2B10* has been determined to be a major contributor to the dexmedetomidine metabolic pathway.[17–19] There have been two clinical studies from James et al. and Fang et al. to date on the relationship between this enzyme and dexmedetomidine pharmacology with no demonstrated association between polymorphisms and PK/PD (Tables 3 and 4).[36,56] The data from James et al.'s cohort was recently incorporated into a genome-wide association study by Shannon et al.[57] Their study found that while about 35% of dexmedetomidine pediatric PK is impacted by pharmacogenomics, there is no significant correlation between dexmedetomidine clearance and any specific single polymorphism (SNP), including *UGT2B10* (Tables 3 and 4).[57]

An alternative cause for variability in patient response is genomic variance at the drug's target receptor; *ADRA2A*. Associations between *ADRA2A* polymorphisms and dexmedetomidine response have been studied in five different distinct homogenous adult populations

(Table 3).[20–58,59] Specifically, in Yaar et al.'s study on adult patients undergoing cardiac surgery, and a separate study from Ding et al. on those undergoing hand surgery, patients with the *ADRA2A* gene polymorphism (rs1800544) had lower sedation scores (indicating higher amounts of sedation) than wild-type (Table 4).[20,59] In contrast, Zhu et al.'s 2019 study of surgical patients showed no difference in sedation scores between groups, but showed a significantly reduced heart rate in the *ADRA2A (*rs1800544) cohort (Tables 3 and 4).[58] These studies provide contradictory results, with reduced sedation (i.e. reduced efficacy) in one cohort, but increased bradycardia (potentially increased adrenergic effect and heightened AEs) in another. Importantly, the study from Zhu et al. did not elaborate on subject's concomitant medications that may have impacted heart rate.[58] Choi et al.'s study in an adult cohort with *ADRA2A* SNPs, including rs1800544, showed no such correlation with sedation, and did not report any data on heart rate (Tables 3 and 4).[22] The link between the rs1800544 polymorphism and dexmedetomidine effect remains unclear. Other *ADRA2A* gene polymorphisms (rs1800035, rs201376588, rs775887911) were studied by Fu et al. in a cohort of women undergoing cesarean delivery.[21] Patients carrying any of these variant alleles had reduced anesthetic and analgesic effect from dexmedetomidine during and after surgery, which was considered statistically and clinically significant (Tables 3 and 4).[21] Of note, there were no cardiovascular or circulatory correlations observed in the cohort.

A study by Fang et al. investigated the relationship between dexmedetomidine PD and polymorphisms of the *GABRA1* and *2* receptors in addition to looking at *ADRA2A* receptor and metabolic enzyme polymorphisms.[56] These alleles play a role in GABAergic neurotransmission; a pathway that alpha-2 agonists have been shown to inhibit.[56,60] This study, conducted in females, found that carriers of the G allele of *GABRA2* rs279847 had a much higher incidence of bradycardia than wild-type patients. These individuals may have reduced *GABRA2* expression, and thus have increased parasympathetic activity downstream of the *ADRA2A* receptor.[56,60] This study found no correlation between *ADRA2A* polymorphisms and pharmacokinetic or pharmacodynamic alterations in patients (Tables 3 and 4).[56]

It is important to note that the cohorts in the above studies were not healthy volunteers and had a wide variety of factors impacting their PK and clinical status. These studies show varying effects of dexmedetomidine in patients with *ADRA2A* SNPs, but do not provide definite causation of AEs or altered sedation. Assessed as a whole, these trials indicate a potential, but weak correlation between *ADRA2A* PGx and clinical outcomes for adults receiving dexmedetomidine for procedural sedation.

Few pediatric studies have been conducted regarding the relationship between PGx and PD effects of dexmedetomidine. Our group studied dexmedetomidine dosing in a PICU cohort and compared cumulative medication burden in patients with *ADRA2A* (rs1800544) polymorphisms.[23] This study found there was no significant correlation between dexmedetomidine response and genotype (Tables 3 and 4).[23] While this study had a relatively low sample size ($n=40$), and included critically ill patients with alterations to PK, it provided the first and only data on *ADRA2A* polymorphisms and dexmedetomidine response in pediatrics.[23,24] Based on this study, there does not appear to be a correlation between *ADRA2A* variants in children and PD effect of dexmedetomidine.

DISCUSSION

Our systematic literature review summarizes information on various pediatric cohorts, ranging from neonates to adolescents, relatively healthy surgical patients to critically ill, and includes studies specific to diseases and procedures, including liver transplant and cardiopulmonary bypass, that affect pediatric patients. Due to low dexmedetomidine clearance in early infancy, neonates and younger infants may have reduced dexmedetomidine demand, independent of weight.[15,32,33] However, providers should be cautioned against empirically under-dosing younger patients. As shown in both Greenberg et al. and Disma et al.'s studies, some infants and children under two require high target plasma concentrations between 1 and 2 ng/mL to achieve target sedation goals.[25,35] Young children appear to display more varied PK than adolescents, with children under 6 years old requiring a wider dosing range (0.2–1.4 μg/kg/h) than children of 6 years old and older (0.2–1.0 μg/kg/h).[46] studies included in this review include a significant number of covariates that were found to impact dexmedetomidine PK and PD in children. The most common of these were patient size and age. A good resource for providers would be the Dutch Pediatric Formulary, which provides weight, age, and target plasma concentration-based dosing for patients older than 1 month of age.[61] These dosing recommendations include procedural sedation and premedication, and prevention of postoperative agitation/delirium.[61] We believe our review adds to this body of knowledge by providing insight on continuous sedation in pediatrics. Based on the data collected, we recommend that providers start at lower doses (0.2–0.4 μg/kg/h) in infants and young children, and titrate up based upon effect (sedation) and tolerance (absence of adverse effects).[38,40,46] Children above 3 years old have demonstrated a higher clearance rate for dexmedetomidine, and based on the studies above, it may

be safe to initiate these patients at 0.4 or even 0.5 μg/kg/h, titrating the dose according to the sedation goal.[32,33,38]

While genotype appears to play a role in the variability of metabolism and PD effect of dexmedetomidine, the current data do not provide strong evidence for genotype-guided dosing. For *ADRA2A*, there has only been one pediatric study conducted, which showed no significant effect of the polymorphic variants on sedation scores, as compared with adults.[23] It is noteworthy that this study had robust polymorphic distribution, with 10 wild-type patients, 15 heterozygous, and 15 homozygous for the rs polymorphic allele rs1800544.[23] While some adult studies have shown an impact of this and other *ADRA2A* polymorphisms on dexmedetomidine's effect,[20,21,58,59] other studies have shown no such difference,[22,56] indicating that dexmedetomidine's PD variability may have one or many different causes. In our systematic review, we have shown that pediatric patients undergoing continuous sedation do not have a tight correlation between dexmedetomidine dose and sedation scores or adverse events,[38,40,41,46] implying that dose alterations do not significantly impact dexmedetomidine's adrenergic effect in this population. Additionally, while there have been some associations between *CYP1A2* and *2A6* and dexmedetomidine pharmacokinetics, no significant pharmacodynamic effects have been shown in studies involving the pediatric population.[14,55] Based on the current evidence, metabolic polymorphisms should not be considered when dosing dexmedetomidine in pediatric patients.

When using dexmedetomidine for the prevention of agitation or delirium, providers should also be aware of the post-surgical delirium risk prediction model by Lin et al.,[45] and screen patients for additive covariates that may increase delirium risk when combined with dexmedetomidine. Children undergoing surgery will also have an altered PK, and third spacing should be accounted for in patients undergoing cardiac bypass.[37] These patients may need higher procedural doses of dexmedetomidine due to a larger Vd.[43]

Several studies have summarized the impact of procedural dexmedetomidine on target organs.[42–44] Pediatric postoperative data are mixed on dexmedetomidine's reno and cardioprotective properties. Jo et al.'s study design was similar to the larger cohort that Kim et al. analyzed for dexmedetomidine-related AKI.[43,44] Kim et al.'s 2020 study failed to demonstrate renal protection, indicating that dexmedetomidine should not be given intraoperatively solely for AKI reduction.[44] Cardiac results from Hassan et al. and Kim et al. are difficult to compare directly, as Kim et al.'s intervention did not include a postoperative dexmedetomidine infusion, and their primary end point did not include cardiac outcomes.[42,44] Unlike their study, Hassan et al.'s trial was designed to identify cardiac outcomes, which may have led to small differences in study design and implementation.[42] Their reduction of JET with dexmedetomidine alone and dexmedetomidine combined with magnesium indicate that the inclusion of perioperative dexmedetomidine may be useful for prevention of JET.[42] Kim et al's study, while not demonstrating JET reduction with dexmedetomidine, showed no increase in adverse event risk when dexmedetomidine is used perioperatively.[44] Finally, this review presents updated data on the potential numeric reduction of dexmedetomidine on analgesic load.[39,43,50] Although the compiled evidence of perioperative dexmedetomidine benefits is weak, it will likely be used more in the pediatric surgical population due to it safety profile. With its growing popularity, it is more important than ever to optimize dexmedetomidine dosing.

Our systematic review also covers specific groups of pediatric patients, including liver transplant and neonates with HIE.[32,34,41] Approximately, 551 pediatric patients per year undergo liver transplants in the United States.[62] Since dexmedetomidine undergoes complete hepatic transformation, these patients will likely have an altered PK and PD response to dexmedetomidine.[34,62] In these patients, it has been found that post-transplantation INR and sedation scores may be the best predictors of dexmedetomidine Cp and PK.[34] This aligns with the FDA biopharmaceutics review, which recommends that dexmedetomidine doses should be reduced in patients with hepatic failure.[16] Providers should consider these covariates, as they may guide dosing better than age and weight in this population.

HIE typically occurs within the first few days of life and is classified as an intrapartum-related hypoxic event, which causes 1 out of every 5 neonatal deaths globally.[63] HIE has a 25% mortality rate in the presence of therapeutic hypothermia, the standard of care.[63,64] McAdams et al. provides data on dexmedetomidine as an alternative to morphine to sedate neonates and prevent shivering.[33] In a case study of seven neonates, reduced overall CL and increased half-life were shown. Despite a small sample size, most patients showed adequate pain and shivering control in response to dexmedetomidine.[32] Elliott et al.'s 2024 cohort of 135 neonates validated these results, providing neonates with adequate comfort and sedation, and significantly decreasing overall opioid exposure.[41] Providers may consider dexmedetomidine for comfort, shivering reduction, and opioid exposure reduction in this population. From a PK perspective, it is important to note that these patients had reduced overall CL and longer half-life, indicating that they may benefit from a lower dose. They also took more time to reach C_{max} (12–24 h), which may have been due to ~5% drug loss via sorptive tubing.[33] Based on study results, neonates with HIE may require a more rapid

titration or use of a loading dose to provide adequate comfort and reduce shivering.

CONCLUSIONS AND FUTURE STUDIES

Although PK and PD studies have increased our understanding of dexmedetomidine dosing in the pediatric population, there remains a wide range of patient-to-patient variability in response, including hypotension and bradycardia. These adverse effects appear more pronounced in continuous sedation than during procedural sedation. While not all studies found significant reductions in analgesic demand, there appears to be a mild anti-analgesic effect produced by dexmedetomidine. Few studies have evaluated the PGx of dexmedotomidine. This review of PGx studies done thus far can be used to guide future genomic research on this drug. *GABRA2* has only been studied in one adult population, and it would benefit the pediatric population to confirm the significance of its correlation with dexmedetomidine pharmacodynamics in the pediatric population. As the primary metabolizing enzyme of dexmedetomidine, *UGT2B10* should be a key target for future research before it is fully ruled out as a covariate. One avenue for investigation of dexmedetomidine pharmacogenomics and kinetics would be PBPK modeling. We found no PBPK models of dexmedetomidine in our search, and this would provide a granular investigation into the physiologic breakdown of dexmedetomidine. For the general pediatric population, weight, age, and clinical status are the most reliable predictors of PK. Special populations and patients receiving procedural vs. continuous sedation may have different dexmedetomidine PK, and different demands for sedation and comfort. The goal is to eliminate uncertainty in dexmedetomidine dosing, reduce the need for titration, and mitigate AEs. Further research, incorporating real-world evidence, PK modeling, and clinical studies, is needed to further guide dosing in this understudied and complex population.

AUTHOR CONTRIBUTIONS

E.T., A.O., S.Q., E.K., and R.B. wrote the manuscript; E.T. and A.O. designed the research; E.T. and A.O. performed the research; E.T., A.O., S.Q., E.K. and R.B. analyzed the data.

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CONFLICT OF INTEREST STATEMENT

The authors declared no competing interests for this work.

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