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ARTICLE

Use of physiologically-based pharmacokinetic modeling to inform dosing of the opioid analgesics fentanyl and methadone in children with obesity

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Abstract

Obesity is an increasingly alarming public health threat, with nearly 20% of children classified as obese in the United States today. Children with obesity are commonly prescribed the opioids fentanyl and methadone, and accurate dosing is critical to reducing the risk of serious adverse events associated with overexposure. However, pharmacokinetic studies in children with obesity are challenging to conduct, so there is limited information to guide fentanyl and methadone dosing in these children. To address this clinical knowledge gap, physiologically-based pharmacokinetic models of fentanyl and methadone were developed in adults and scaled to children with and without obesity to explore the interplay of obesity, age, and pharmacogenomics. These models included key obesity-induced changes in physiology and pharmacogenomic effects. Model predictions captured observed concentrations in children with obesity well, with an overall average fold error of 0.72 and 1.08 for fentanyl and methadone, respectively. Model simulations support a reduced fentanyl dose (1 vs. 2 μg/kg/h) starting at an earlier age (6 years) in virtual children with obesity, highlighting the importance of considering both age

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and obesity status when selecting an infusion rate most likely to achieve steady-state concentrations within the target range. Methadone dosing simulations highlight the importance of considering genotype in addition to obesity status when possible, as cytochrome P450 (*CYP*)*2B6*6/*6* virtual children with obesity required half the dose to match the exposure of wildtype children without obesity. This physiologically-based pharmacokinetic modeling approach can be applied to explore dosing of other critical drugs in children with obesity.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Nearly 20% of children in the United States are classified as obese. Although the opioids fentanyl and methadone are commonly dosed in these children, obesity-induced changes in their exposure are not well understood.

WHAT QUESTION DID THIS STUDY ADDRESS?

Physiologically-based pharmacokinetic models were developed and scaled to children with obesity to evaluate the interplay of obesity, age, and genetic variation in the exposure of fentanyl and methadone and to avoid serious adverse events associated with overexposure.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

Fentanyl model simulations confirm increased exposure with obesity in children and highlight the importance of considering both age and obesity status when selecting an infusion rate most likely to achieve target concentrations. Methadone dosing simulations highlight the importance of considering genotype when possible and show that cytochrome P450 (*CYP*)*2B6*6/*6* children with obesity are at greatest risk of overexposure.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?

This physiologically-based pharmacokinetic modeling approach can be applied to inform dosing of other drugs commonly used in children with obesity.

INTRODUCTION

Nearly one in five children are obese in the United States, and almost 10% of children worldwide have obesity today.[1–3] The prevalence of childhood obesity is growing, as obesity rates in US children nearly quadrupled in the past 25 years alone. This is an alarming public health issue. Children with obesity require significantly more prescription drugs than children without obesity, which must be dosed appropriately given increased body size.[4,5] Recommended dosing in children is often weight-based (e.g., in mg/kg), and thus children with obesity frequently receive higher absolute doses (e.g., in mg) than children without obesity. This means that the maximum (adult) dose can be reached at very young ages in children with obesity. In addition, many drugs are known to have altered clearance or volume of distribution with obesity, with one review finding 65% of drugs under study demonstrated clinically significant pharmacokinetic (PK) alterations.[6] Despite this, the effect of obesity on the dosing of many drugs in children is poorly understood, with few US Food and Drug Administration labels providing dosing guidance in this population.[7]

PK clinical studies are challenging to conduct in children with obesity in particular, as a stigma can further lower enrollment rates, hindering the ability to enroll the full age and body size range of children needed to evaluate drug disposition. Physiologically-based pharmacokinetic (PBPK) modeling can be useful given these challenges to prospective data collection. PBPK modeling integrates physiological variables, drug-related properties, and study design elements (e.g., dosing regimens) to mechanistically describe drug exposure.[8,9] It is an especially useful modeling tool for evaluating pediatric obesity dosing considerations because it can account for obesity-induced changes in physiology to account for

altered drug disposition and predict pharmacokinetics (PKs) in children with obesity.[10] Even in the absence of any available clinical data, PBPK modeling allows for exploration of the interplay between various factors that can impact PKs, including age, body size, and genotype.[10] PBPK modeling has previously been used to characterize the PKs of eight drugs in adults with obesity.[11] In addition, a recently developed virtual population of children with obesity incorporating key obesity-induced physiological changes (including increased organ size, blood flow, and elimination processes) was used to describe the PKs of trimethoprim/sulfamethoxazole and clindamycin.[12] However, this approach has not been systematically applied to evaluate dosing of other drugs commonly used in children with obesity, including opioid analgesics.

Fentanyl and methadone are commonly dosed analgesic drugs in children with obesity. Fentanyl is indicated for analgesia and sedation in children older than 2 years in the United States. However, methadone's product labeling in the United States states that the PKs, safety, and efficacy have not yet been established in children despite being commonly prescribed for neonatal abstinence syndrome, the opioid weaning process, and severe pain.[13–16] Appropriate dosing of these drugs in children of all sizes is vitally important, as oversedation is associated with serious adverse outcomes such as respiratory depression, prolonged use of mechanical ventilation, and longer pediatric intensive care unit stays.[17] Children with obesity are at even greater risk of the respiratory adverse effects of opioids that occur with overdosing, and obesity is a risk factor for procedural sedation complications.[18,19] Despite these risks, PK studies in patients (adults or children) with obesity for either drug are rare. A population PK study of children with obesity receiving fentanyl identified modified infusion rates based on total body weight to reduce the risk of overexposure in these children.[20] In addition to age and obesity, genetic variation plays a role in the high PK variability displayed by methadone. Genetic variants in cytochrome P450 (*CYP*)*2B6*, a major elimination route of methadone, particularly the **4* and **6* alleles, have displayed increased and decreased methadone clearance, respectively, in adults.[21–24] However, the potential interplay between age, obesity status, and *CYP2B6* genotype has yet to be explored.

The objective of this study was to leverage PBPK modeling to evaluate dosing considerations for fentanyl and methadone in children with obesity (after incorporating pharmacogenomic effects) to better inform the dosing of these analgesics in these children. To achieve this objective, PBPK models for both drugs were scaled to children and then evaluated using data in children with and without obesity.

METHODS

Data sources for PBPK models

Observed concentrations for healthy adult volunteers were digitized from literature studies when available for model development using Graph Grabber© (version 2.0; Quintessa; quintessa.org). Individual-level concentration data were available for fentanyl and methadone for children with and without obesity from the "Pharmacokinetics of Understudied Drugs Administered to Children Per Standard of Care" (Pharmacokinetics of Understudied Drugs Administered to Children per Standard of Care study [POP01]; ClinicalTrials.gov no. NCT01431326) and the "Pharmacokinetics of Multiple Dose Methadone in Children Treated for Opiate Withdrawal" (Pharmacokinetics of Multiple Dose Methadone in Children Treated for Opiate Withdrawal study [MTH01]; ClinicalTrials.gov no. NCT01945736) clinical trials. Both were prospective, open-label PK and safety studies enrolling children receiving drugs per standard of care. The POP01 study enrolled children aged <21 years, whereas the MTH01 study enrolled children <18 years. Institutional review boards (IRBs) approved each study at the participating centers, and parental guardian consent was obtained for each patient. The IRB approved the PBPK modeling described herein at the University of North Carolina at Chapel Hill. Because the analysis was focused on children with clearly defined obesity, pediatric patients in both studies aged younger than 2 years were excluded. In addition, patients on extracorporeal membrane oxygenation were excluded from the analysis. Children with a body mass index (BMI) ≥95th percentile were considered obese, as defined by the 2000 Centers for Disease Control and Prevention growth charts.[25] Extended BMI percentile, which is calculated as the BMI percentile for a child's given age and sex divided by 95%, was used as a further classification of obesity, where a child with an extended BMI percentile ≥100% has obesity.[25] A summary of clinical studies used in this work is shown in Table S1.1. Additional details for the methadone POP01 and MTH01 trials can be found in Section S3.2, and the fentanyl data collection through the POP01 trial has been previously described.[20] Between the two studies, there were 223 samples available for 35 children without obesity and 180 samples available for 52 children with obesity (Table 1).

PBPK model development

This study followed the recommended PBPK model development process outlined here (Figure S1.1).[26] First,

TABLE 1 Population demographics for pediatric subjects receiving either fentanyl or methadone in the POP01 and MTH01 studies

Demographics	Children without obesity (*N* = 35)	Children with obesity (*N* = 52)	Combined (*N* = 87)
n, samples	223	180	403
Age, years	7.9 (2.1, 19.0)	12.7 (2.1, 19.7)	10.3 (2.1, 19.7)
Age groups			
2–<6 years	13 (37.1%)	10 (19.2%)	23 (26.4%)
6–<12 years	11 (31.4%)	15 (28.8%)	26 (29.9%)
12–18 years	11 (31.4%)	27 (51.9%)	38 (43.7%)
Male	16 (45.7%)	27 (51.9%)	43 (49.4%)
Weight, kg	23.6 (8.1, 82.0)	64.8 (14.3, 164.4)	42.0 (8.1, 164.4)
Height, cm	75.5 (123.0, 180.0)	151.0 (81.0, 189.0)	136.0 (75.5, 189.0)
BMI, kg/m^2	16.3 (12.7, 30.1)	27.2 (18.4, 62.11)	23.5 (12.7, 62.1)
BMI percentile, %	28.6 (0, 94.1)	99.1 (95.0, 100.0)	96.6 (0, 100.0)
Extended BMI percentile, %	78.5 (50.2, 97.1)	122.2 (100.0, 257.0)	50.2 (103.3, 257.0)
Weight classification[a]			
Without obesity	35 (100%)	0 (0%)	35 (40.2%)
With obesity, Class I	0 (0%)	25 (48.1%)	25 (28.7%)
With obesity, Class II	0 (0%)	14 (26.9%)	14 (16.1%)
With obesity, Class III	0 (0%)	13 (25.0%)	13 (14.9%)
Race			
White	25 (71.4%)	37 (71.2%)	62 (71.3%)
Black or African American	7 (20%)	11 (21.2%)	18 (20.7%)
Asian	0 (0%)	0 (0%)	0 (0%)
American Indian/Alaskan Native	0 (0%)	0 (0%)	0 (0%)
Native Hawaiian/Pacific Islander	0 (0%)	0 (0%)	0 (0%)
Other	0 (0%)	0 (0%)	0 (0%)
Multiple races	3 (8.6%)	2 (3.8%)	5 (5.7%)
Unknown/not reported	0 (0%)	2 (3.8%)	2 (2.3%)
Ethnicity			
Hispanic/Latino	4 (11.4%)	4 (7.7%)	8 (9.2%)
Not Hispanic/Latino	31 (88.6%)	47 (90.4%)	78 (89.7%)
Unknown/not reported	0 (0%)	1 (1.9%)	1 (1.1%)
Drug received			
Fentanyl	2 (5.7%)	30 (57.7%)	32 (36.8%)
Methadone	33 (94.3%)	22 (42.3%)	55 (63.2%)

Values are medians (range) for continuous variables and counts (%) for categorical variables.

Abbreviations: BMI, body mass index; MTH01, Pharmacokinetics of Multiple Dose Methadone in Children Treated for Opiate Withdrawal study; POP01, Pharmacokinetics of Understudied Drugs Administered to Children per Standard of Care study.

[a]Weight classifications are assigned using conventional definitions: extended BMI percentile <100% is without obesity, 100%–<120% is Class I obesity, 120%–<140% is Class II obesity, and ≥140% is Class III obesity.

available drug physicochemical and adult physiological information was integrated to develop adult PBPK models. Adult PBPK models were then evaluated with digitized concentration versus time data to gain confidence in the model structure and parameterization before scaling to children. Next, adult PBPK models were scaled to children without obesity using known age-dependent changes in anatomy and physiology, including enzyme ontogeny. These models were evaluated using digitized or on-hand concentration data in children without obesity. To expand the pediatric PBPK models to include children with obesity, a published virtual population of children with obesity that incorporates known pediatric obesity-induced physiological changes was used.[12] The models

were again evaluated using digitized or individual-level concentration data for children with obesity. Last, the final pediatric PBPK models were used to simulate exposure in children with versus without obesity to evaluate dosing regimens in these children under various clinical scenarios. By developing and evaluating the PBPK models in this stepwise fashion (i.e., adults, children without obesity, children with obesity), greater confidence in model structure is obtained in populations for which there is more available physiologic and drug concentration data (i.e., adults) before moving to populations with less available information (i.e., children with obesity). Sections S2 and S3 of the Supporting Information describe the full details of the model development processes, which are summarized next.

PBPK models were developed in PK-Sim® (version 8; Open Systems Pharmacology Suite; open-systems-pharmacology.com). Whole-body adult PBPK models were developed by incorporating known physicochemical, clearance, and absorption properties. Perfusion-rate limitations were assumed, with each compartment represented as well-stirred. The fentanyl model included both CYP3A4 and CYP3A5 metabolism. Pharmacogenomic data for fentanyl remains limited, so no CYP3A4 or CYP3A5 pharmacogenomic effect was implemented in the fentanyl PBPK model.

For the methadone PBPK model, renal elimination and metabolism via CYP2B6, CYP2C19, and CYP3A4 were included. Enantiomeric differences in elimination pathways (i.e., fraction metabolized/renally eliminated) were included for both the R- and S-methadone enantiomer, as R-methadone is responsible for efficacy, whereas S-methadone can contribute to known adverse events. Observed metabolite concentrations were used to evaluate methadone's primary, inactive CYP metabolite, ethylidene-1,5-dimethyl-3,3,-diphenylpyrrolidine (EDDP). In addition, anticipated pharmacogenomic effects of *CYP2B6* variants were included in the adult model using digitized data from a previously published methadone pharmacogenomics study in adults.[23] This study included data from patients with the *CYP2B6*6/*6* genotype, associated with slower clearance, as well as those with a **4* variant, associated with faster clearance.[23] Additional pharmacogenomic effects (e.g., CYP3A4) were not included, as previous studies highlight the role of CYP2B6 as the primary driver of genetic variability in methadone exposure.[22,24,27,28]

The adult models were scaled to pediatric populations following adult model evaluation by scaling glomerular filtration (renal clearance), metabolic enzyme concentration, and binding protein concentration using known ontogeny functions. PK-Sim® pediatric virtual populations with and without obesity include relevant physiological parameters, including changes from adults in body weight, height, organ volumes and blood flows, and tissue composition. Virtual children with obesity had increased overall body weight as determined by updated BMI-for-age growth curves and increased lean body weight, organ volume, blood flow, and corresponding effects on clearance processes as previously described.[12] Detailed drug-specific information for each model, including model parameter tables, is described in Sections S2 and S3 of the Supporting Information. In addition, project files for the methadone and fentanyl PBPK models are available as Supporting Information.

PBPK model evaluation

For both adult and pediatric PBPK model evaluation, virtual populations of 250 virtual subjects were generated based on patient demographics from the corresponding digitized study. Because both the POP01 and MTH01 studies included wide variations in dosing, a simulation was performed for each subject using "individualized" populations matched to each particular subject's demographics and dosing regimen. PBPK predictions were evaluated by calculating the number of observed concentrations falling within the 90% model prediction interval as well as by calculating the average fold error (AFE) of the median simulated concentration for all samples according to Equation (1):

$$\mathrm{AFE} = 10^{\frac{1}{n}\sum \log\left(\frac{\text{predicted}}{\text{observed}}\right)} \quad (1)$$

where n is the total number of samples for a particular subject (or digitized study). Model acceptance criteria included visually assessing overlaid digitized and observed data with the 90% model prediction interval for the appropriate fit, assuring that simulated PK parameters were within 50% of the reported values, and achieving AFE within 0.5- to 2-fold.

PBPK model dosing simulations

First, a series of population simulations ($n = 1000$ virtual children with and without obesity across a full, normally distributed body size range) was performed for each drug using the recommended dosing outlined herein to evaluate how absolute and weight-normalized clearance and volume of distribution change with increasing extent of obesity. Dosing adjustments designed to achieve comparable exposure between children with and without obesity were explored when required to match exposure to

children without obesity, defined as median exposure within ±25% for each age group (2–<6 years, 6–<12 years, and 12–18 years, which are standard age classifications for early childhood, middle childhood, and adolescence, respectively).[29] Next, population simulations (n = 1000 virtual children for each group) were performed to understand how well current recommended pediatric dosing for each drug achieves target exposure in children with obesity.

Fentanyl dosing of 1, 2, and 3 μg/kg/h continuous infusions over 240 h was simulated for each age group.[20] A previously described target steady-state plasma concentration (C_{ss}) range of 1–3 ng/ml was used that was previously found to be effective for providing analgesia in postoperative adults and critically ill children.[30–33] Concentrations above this range have been previously associated with significant levels of respiratory depression in adults.[30] However, no pediatric exposure target has been formally established for fentanyl, as dosing is mainly dependent on individual patient response to treatment.[30–33]

For methadone, typical oral dosing of 0.2 mg/kg every 8 h was simulated for each age group, and a dose cap of 10 mg/dose was explored.[16,34,35] There are no established pediatric exposure targets for methadone. Thus, the 90% prediction interval for the steady-state trough concentration ($C_{ss,min}$) for *CYP2B6* wildtype children without obesity was used as the target range for children with obesity as well as to evaluate the influence of genotype for children with a variant *CYP2B6* genotype. An additional target of a $C_{ss,min}$ ≥30 ng/ml, the minimum effective concentration (MEC) reported for adult perioperative and cancer pain patients, was evaluated in all pediatric subgroups.[34,36,37] Note that the recommended dosing stated previously for both drugs is not specific for children with obesity but is weight based.

The ability of the aforementioned dosing strategies for fentanyl and methadone to achieve a specified target exposure was evaluated using a probability-based approach.[20] Individual estimates of the drug exposure (i.e., C_{ss} for fentanyl; $C_{ss,min}$ for methadone) were calculated from each virtual subject included in the dosing simulations. Then, the probability of a specific dosing strategy achieving a drug exposure within a set target range was solved by integration using Equation (2):

$$P\left(a \le C_{ss} \text{ or } C_{ss,min} \le b\right) = \int_a^b f(x)\mathrm{d}x \qquad (2)$$

where $P(a \le C_{ss}$ or $C_{ss,min} \le b)$ is the probability of a given measure of drug exposure falling within a lower (a) and upper (b) limit, and $f(x)$ denotes the lognormal probability density function for the given exposure metric. Integrating from 0 to the lower bound (a), a to the upper bound (b), and b to infinity, the probability for virtual children to obtain a given measure of exposure below, within, or above the desired range, respectively, is obtained. Probability assessments were computed by extended BMI percentile to understand how these probabilities change with an increasing extent of obesity.

RESULTS

Adult PBPK model development and evaluation

The adult PBPK models for fentanyl and methadone captured digitized adult concentration versus time data well, with AFEs of 0.95 and 0.80 (0.73, 0.82, 0.69, and 0.98 for methadone, R-methadone, S-methadone, and EDDP, respectively) across digitized studies (Figure 1). After incorporating changes in clearance with *CYP2B6* genotype, the AFE for *CYP2B6*6/*6* adult subjects was 1.03, 0.63, and 1.27 for R-methadone, S-methadone, and EDDP, respectively. Fentanyl and methadone model-predicted adult PK parameters were within twofold of reported values.

Pediatric PBPK model scaling and evaluation

For children without obesity, the fentanyl and methadone models captured observed, individual-level concentration data well, with AFEs of 0.68 and 1.36 (1.32, 0.97, 0.89, and 1.93 for methadone, R-methadone, S-methadone, and EDDP, respectively; Figure 2). For methadone, 63.6% (63.3%, 82.5%, 94.7%, and 42.2% for methadone, R-methadone, S-methadone, and EDDP, respectively) fell within the 90% prediction interval.

The PBPK models also captured observed individual-level concentration and reported PK parameter data well for children with obesity. The fentanyl model had an AFE of 0.72, with 52.0% of observed concentrations falling within the 90% prediction interval (32.0% above, 16.0% below). The methadone model had an AFE of 1.08 (0.58, 1.09, 1.12, and 1.42 for methadone, R-methadone, S-methadone, and EDDP, respectively), with an overall 64.6% (32.0%, 85.2%, 84.6%, and 59.6% for methadone, R-methadone, S-methadone, and EDDP, respectively) of samples falling with the 90% prediction interval. AFE by genotype was within twofold for both children without and with obesity (1.31 and 0.88 for *CYP2B6* wildtype and **6/*6* genotypes, respectively). See the Supporting Information for full details on the model development and evaluation of both drugs in adults and children.

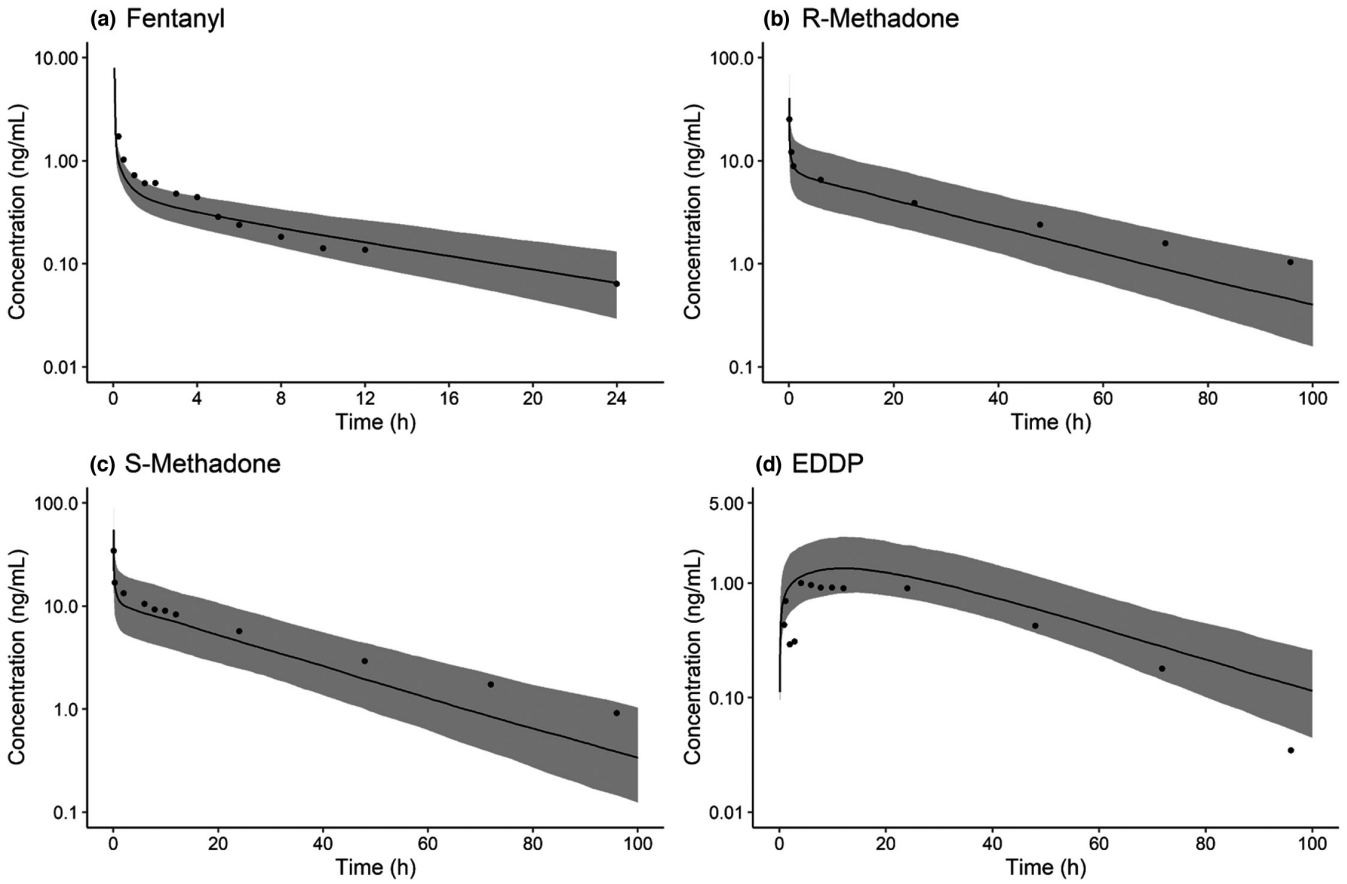

FIGURE 1 Population simulations ($n = 500$ each) of (a) fentanyl, (b) R-methadone, (c) S-methadone, and (d) EDDP digitized from studies of adults receiving an intravenous dose.[47,48] Subjects received either a 5 μg/kg intravenous bolus dose of fentanyl or a 5.4 mg intravenous dose of methadone. Shaded regions represent the 90% model prediction interval, the solid line represents the median simulated concentration, and points are digitized observed concentrations. See Figures S2.1 and S3.1 for all adult simulations used to evaluate the fentanyl and methadone physiologically-based pharmacokinetic models, respectively. EDDP, 2-ethylidene-1,5,-dimethyl-3,3-diphenylpyrrolidine

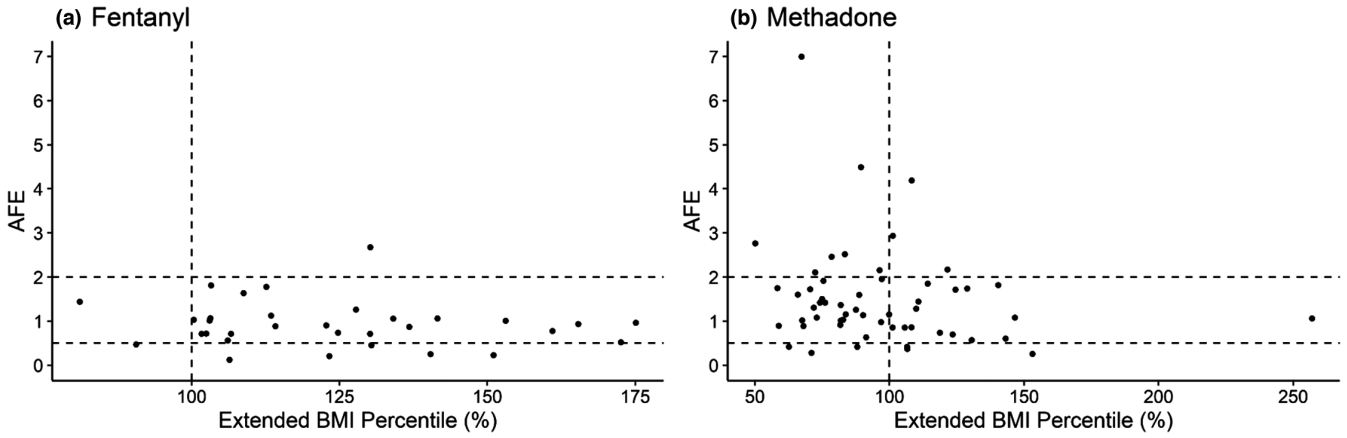

FIGURE 2 AFE for pediatric subjects with and without obesity who received either (a) fentanyl or (b) methadone plotted versus extended BMI percentile. The horizontal dashed lines represent twofold error, and the vertical dashed line represents the cutoff for obesity for reference. AFE was calculated using median simulated concentration. Extended BMI percentile is calculated as the BMI percentile for a subject's age and sex divided by 95%, where children with an extended BMI percentile ≥100% are considered obese. AFE, average fold error; BMI, body mass index

Dosing simulations

Across both drugs, steady-state absolute clearance and volume of distribution increased with increasing body size for each age group, whereas weight-normalized clearance and volume of distribution decreased (Figure 3). Increases in absolute clearance attributable to increased kidney volume (and thus glomerular filtration rate) in children with obesity did not increase to the same degree as body weight; therefore, weight-normalized clearance decreased.

The probability of attaining a target fentanyl C_{ss} within 1–3 ng/ml following a continuous infusion was greatest for 1 μg/kg/h dosing considering all virtual pediatric subjects pooled together (Figure 4). These results were comparable with virtual adults of a standard 70 kg weight, where 86.6% were within the target concentration range (with 12.7% below and 0.7% above) following a 1 μg/kg/h infusion. However, probability-based analyses per subgroup revealed important differences with both age and obesity status. An optimal dose of 2 and 1 μg/kg/h for ages 2–<6 years and 12–18 years, respectively, was found to have the greatest probability of target attainment independent of obesity status (Table 2). For the age group of 6–<12 years, however, the optimal dose differed by obesity status. For children aged 6–<12 years without obesity, the model recommends 2 μg/kg/h, whereas 1 μg/kg/h is best for children aged 6–<12 years with obesity.

Methadone PBPK model simulations suggest that across all virtual subjects, irrespective of age, body size, and genotype status, 99.0% were above the MEC. However, comparing pediatric subgroups to *CYP2B6* wildtype children without obesity exposure reveals that these groups are at different risks of overexposure (Figure 5). The risk of overexposure increased only slightly with increasing obesity, but this risk was more pronounced and increased to a greater degree for *CYP2B6*6/*6* children with obesity. *CYP2B6*6/*6* virtual children in general exhibited a greater risk of overexposure relative to wildtype children, and halving the recommended weight-based dose significantly reduced this risk, leading to far better exposure matching. There were no significant differences between age groups.

DISCUSSION

We developed and scaled PBPK models of fentanyl and methadone to children with and without obesity to evaluate how obesity impacts recommended dosing for these analgesic drugs in children and to better understand the interplay between age, genotype, and obesity. At present, only one other study used PBPK models to evaluate dosing in children with obesity, and that study evaluated different drugs (clindamycin and trimethoprim/

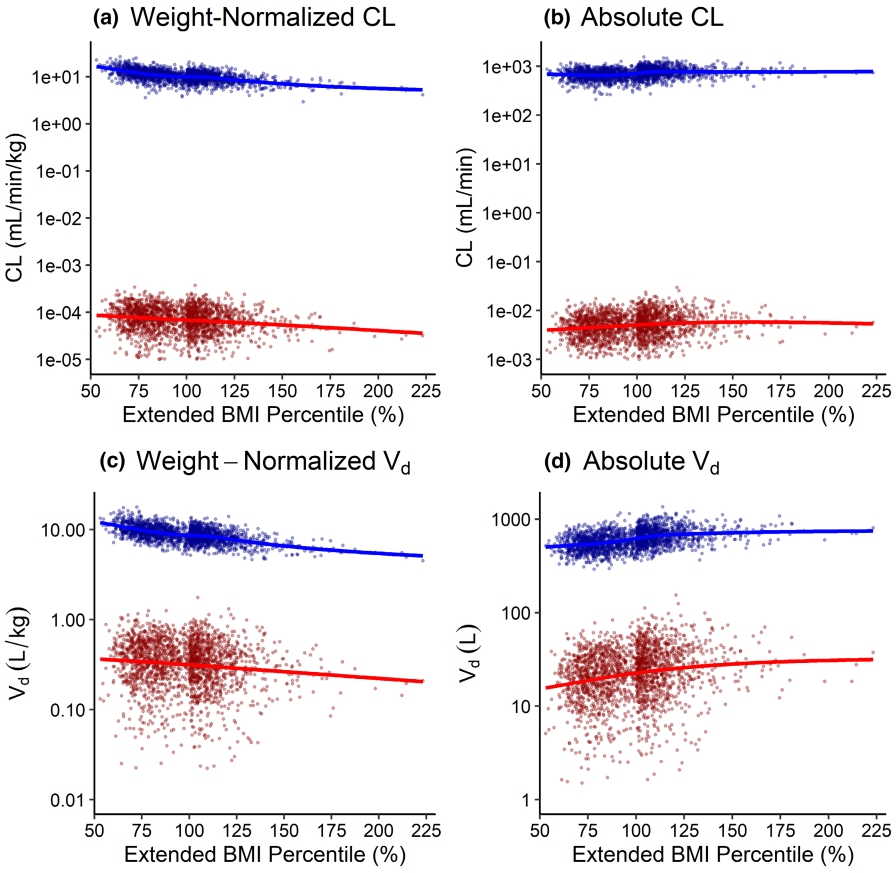

FIGURE 3 Changes in simulated fentanyl (blue) and methadone (red) weight-normalized and absolute CL (a, b) and V_d (c, d) with increasing body size or extended BMI percentile for virtual children aged 12–18 years with and without obesity. Extended BMI percentile is calculated as BMI percentile for a subject's age and sex divided by 95%, where children with an extended BMI percentile ≥100% are considered obese. Virtual children received a 1 μg/kg/h intravenous fentanyl dose infused over 240 h or a 0.2 mg/mg oral methadone dose. Points represent values for individual virtual children ($n = 1000$ for each subgroup). Lines represent the central tendency, which is the Loess line as calculated by the generalized additive model. Similar plots for the age groups 2–<6 years and 6–<12 years can be found in Figures S1.2–S1.3. BMI, body mass index; CL, clearance; V_d, volume of distribution

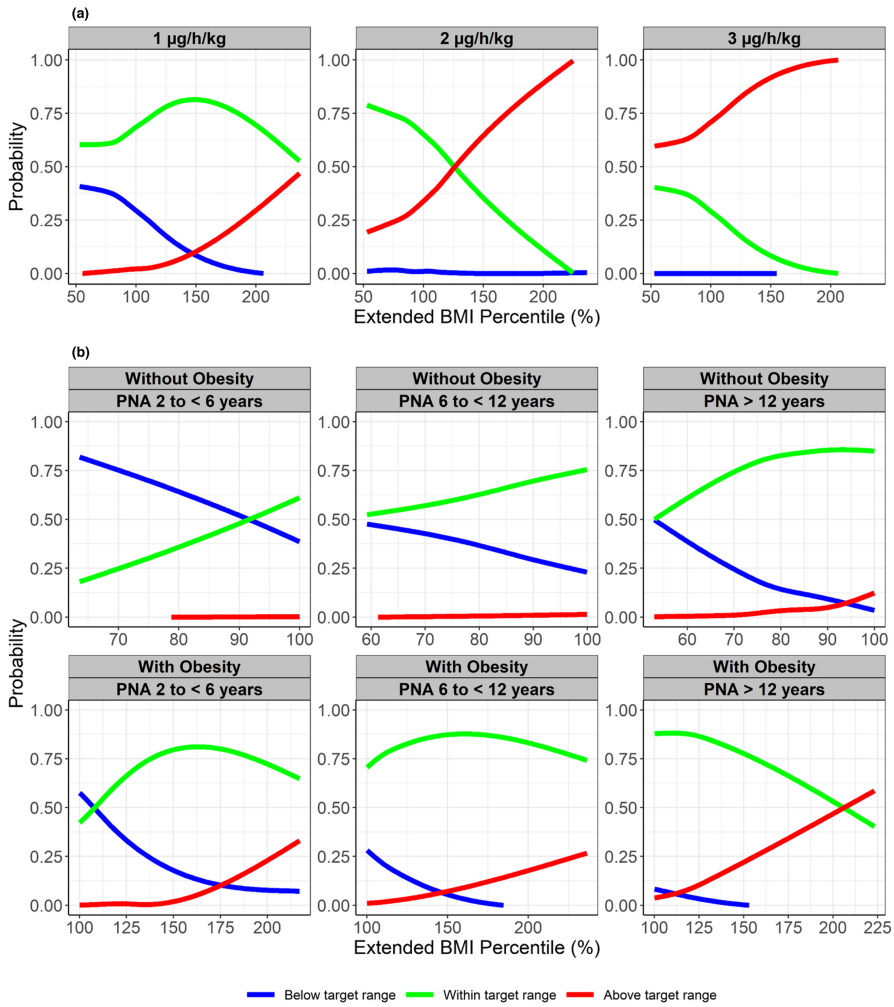

FIGURE 4 Probability of being above, within, or below target fentanyl concentrations of 1–3 ng/ml with increasing extended BMI percentile.[30–33] (a) Probabilities for pooled subjects (children with and without obesity 2–18 years of age; $n = 1000$ for each subgroup) receiving a 1, 2, or 3 µg/h/kg intravenous fentanyl infusion over 240 h. (b) Probabilities for virtual children receiving a 1 µg/h/kg intravenous fentanyl infusion broken down by both age and obesity status. Extended BMI percentile is calculated as BMI percentile for a subject's age and sex divided by 95%, where children with an extended BMI percentile ≥100% are considered obese (similar plots for 2 and 3 µg/kg/h can be found in Figures S2.8–S2.9). BMI, body mass index; PNA, postnatal age

TABLE 2 Summary of PBPK model-derived recommended dosing for fentanyl and methadone

	2–<6 years	6–<12 years	12–18 years
Dosing needed to achieve simulated fentanyl exposure between 1–3 ng/ml			
Children without obesity	2 µg/kg/h	2 µg/kg/h	1 µg/kg/h
Children with obesity	2 µg/kg/h	1 µg/kg/h	1 µg/kg/h
Dosing needed to match simulated methadone exposure for wildtype *CYP2B6* children without obesity			
Children with obesity: *CYP2B6* wildtype	0.2 mg/kg	0.2 mg/kg	0.2 mg/kg
Children without obesity: *CYP2B6*6/*6*	0.1 mg/kg	0.1 mg/kg	0.1 mg/kg
Children with obesity: *CYP2B6*6/*6*	0.1 mg/kg	0.1 mg/kg	0.1 mg/kg

Abbreviations: CYP, cytochrome P450; PBPK, physiologically-based pharmacokinetic.

sulfamethoxazole).[12] PBPK modeling in that study supported recommended dosing of clindamycin and trimethoprim/sulfamethoxazole in children with obesity despite decreased weight-normalized clearance and higher absolute doses with weight-based dosing.[12] The present study highlights the importance of considering age (fentanyl) and genotype (methadone) to optimize dosing per patient subgroup. This is especially important for these opioids, as overdosing leads to serious adverse events.

A fentanyl PBPK model was developed that adequately captured digitized adult concentrations and PK parameters. Metabolism of fentanyl via CYP3A4 was described using a literature fentanyl in vitro maximum rate of metabolism (V_{max}) value obtained from a microsomal assay

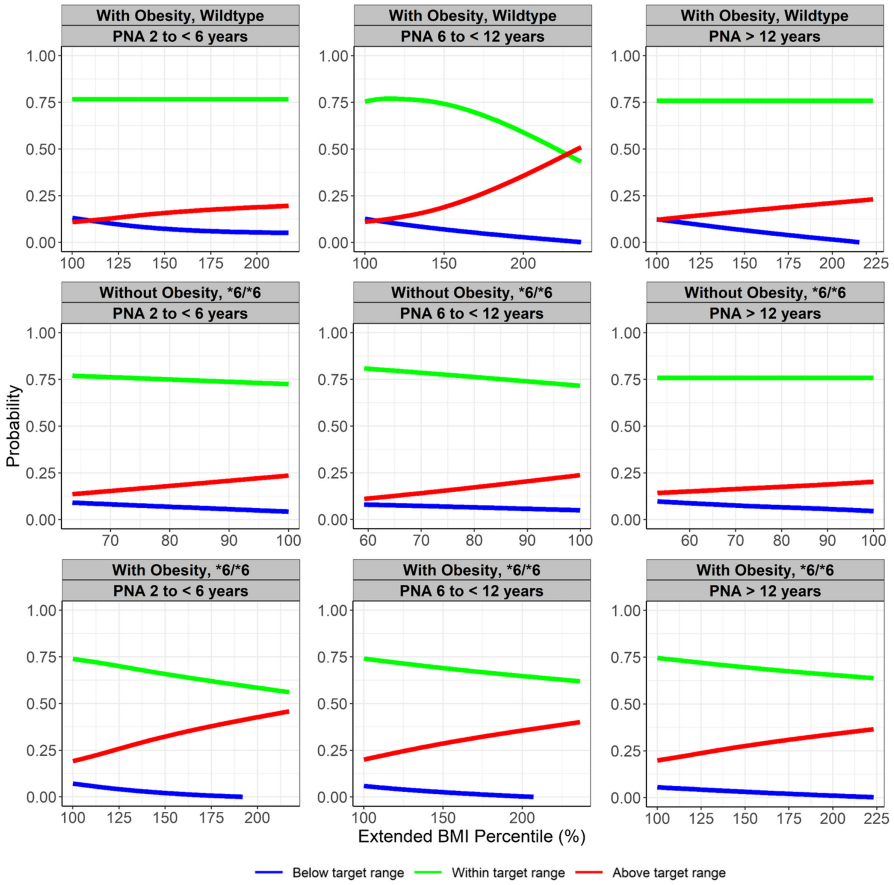

FIGURE 5 Probability of being above, within, or below the 5th–95th percentile of methadone steady-state trough concentration of age-matched *CYP2B6* wildtype children without obesity versus extended BMI percentile for children aged 2–<6 years, 6–<12 years, and 12–18 years ($n = 1000$ per subgroup). The first row includes cytochrome P450 (*CYP*)*2B6* wildtype children with obesity with varying ages, whereas the second and third rows include *CYP2B6*6/*6* children without and with obesity, respectively. Virtual children received a 0.2 mg/kg oral dose of methadone. The extended BMI percentile is calculated as BMI divided by the 95th BMI percentile for a virtual subject's age and sex, where children with an extended BMI percentile ≥100% are considered obese. BMI, body mass index; PNA, postnatal age

and scaled to an in vivo V_{max} value using CYP3A4 protein content in liver microsomes.[38] Specific CYP3A5 clearance was optimized based on adult digitized data, and renal clearance was fixed to literature values.[39] When evaluating the model in children with obesity, a significant number of concentrations fell outside the 90% model prediction interval. This may be attributed to the significant heterogeneity of the data set, which was obtained using opportunistic sampling from hospitalized children.

Model simulations performed using virtual populations of children with and without obesity showed that fentanyl absolute clearance increases with obesity. This might be related to increases in liver size and absolute liver blood flow that were incorporated in virtual children with obesity and is in agreement with literature reporting that patients with obesity have an increase in circulating blood volume and an increase in cardiac output.[12] In a pilot study, Vaughns et al. investigated the PKs of fentanyl after a 5 μg/kg intravenous bolus administration in six adolescents with severe obesity.[18] Fentanyl absolute clearance was increased compared with literature data from children and adults without obesity.[31,32,40] In addition, when normalized by total body weight, the simulations demonstrated that weight-normalized clearance for fentanyl decreased with obesity. In fact, a fentanyl population PK model that evaluated 30 children with obesity found an inverse association between post hoc weight-normalized clearance values and obesity classification.[20] The weight-normalized volume of distribution decreased with obesity in alignment with these findings, which could be attributed to the higher body fat mass in children with versus without obesity.[20]

Together, the differences in weight-normalized clearance and volume of distribution in children with and without obesity suggest that similar weight-based infusion regimens can result in higher fentanyl C_{ss} in children with obesity. Model simulations investigating the probability of three different fixed-rate dosing infusion regimens to achieve C_{ss} values within the target range demonstrated that children with obesity require a lower fixed-rate infusion regimen to achieve the target C_{ss}. The optimal dosing regimen depends not only on the obesity status but also on age. A similar approach was used by Maharaj et al.[20] using post hoc clearance estimations derived from a population PK approach. However, because that model did not consider age, the recommended fixed dosing regimen of 1 μg/kg/h may not be enough for children in the youngest age group (2–<6 years).[20]

A methadone PBPK model was developed using pharmacogenomic adult data to scale and characterize differences in exposure by *CYP2B6* genotype in children.[23] Although in vitro *CYP2B6* activity data for CYP2B6

variants were not available to inform the model, optimizing CYP2B6 clearance based on digitized concentration data from adults of various *CYP2B6* genotypes allowed for describing pharmacogenomic effects in children by leveraging adult clinical data. Ontogeny of the different methadone elimination routes was included, but not likely to play a role in the differences in PK with obesity or genetic variation given that the focus of this study was on children aged older than 2 years. The model tended to overpredict metabolite concentrations for both children with and without obesity, which may be attributable to other additional minor metabolic pathways for methadone that were not included. PBPK-predicted clearance and volume of distribution were within twofold of previous clinical studies conducted in children and adolescents with more intensive sampling.[16,35,41,42] The PBPK model failed to capture concentrations for two children with a *CYP2B6*4* variant, likely because *CYP2B6*4* variant adult data were derived from only four subjects. Although the *CYP2B6*6* variant occurs in 15%–60% of different human populations, the *CYP2B6*4* variant occurs far less frequently (0%–5%).[43] Thus, virtual children with a *CYP2B6*4* variant were not included in dosing simulations.[23]

Although nearly all virtual children achieved the MEC derived from adult patients, there were differences in methadone exposure by genotype and obesity status. There is currently no established upper target concentration for methadone, although overexposure can lead to severe adverse events, such as respiratory depression, QT interval prolongation, and serious arrhythmia. Without a better target, we evaluated the probability of exceeding methadone exposure of *CYP2B6* wildtype children without obesity. The risk of simulated overexposure increased slightly with increasing obesity, but this risk was much more pronounced and increased to a greater degree for *CYP2B6*6/*6* children with obesity.[18] Model simulations suggest halving the recommended weight-based dose for these children. However, in clinical practice, genotype information for pediatric patients before dose initiation is rarely available. These simulations shed light on methadone's high patient interindividual variability and highlight *CYP2B6* genotype as a key driver of this variability over obesity status or age group. Smaller changes in overexposure by age group or obesity status suggest that weight-based methadone dosing and dose monitoring is likely adequate in the absence of better target concentrations or genotype information. Furthermore, the interplay of obesity and genetic variation in *CYP2B6* should be further explored, as these dosing simulations show that virtual *CY2B6*6/*6* children with obesity were at the highest risk of overexposure (Figure 5).

Although this study aims to better understand key dosing elements in children with obesity, a critically underserved patient population, some noteworthy limitations exist. Using PBPK modeling can overcome some of the challenges related to limited data available in pediatrics, as this approach is less dependent on larger data sets common to more traditional modeling techniques. Disease state or pathophysiology for pediatric subjects, particularly any potential comorbidities for children with obesity, were not known or accounted for in the PBPK models. Children included in this study were likely intensive care unit patients, trauma patients, or patients with pain (e.g., from cancer or sickle cell). Any physiological differences between these patient groups are not included, and some of these groups may have an underrepresentation of obesity. This study focuses only on PKs and does not account for age- and obesity-related differences in pharmacodynamics, such as reduced mu-opioid brain receptor activity or reduced airway volume associated with obesity.[44–46] The two drugs presented in this study do not represent the full spectrum of drugs that are used in children with obesity, and exposure and dosing trends presented here may not translate to other drugs dosed in these children. Although weight-normalized clearance and volume of distribution decreased at relatively similar rates with increasing body size for these two drugs, which have similar high lipophilicities and exhibit major CYP elimination pathways, the magnitude of these changes is likely not constant across all drugs as previously suggested.[6,12] However, this study sheds further light on how to personalize dosing across pediatric subgroups with varying obesity status, age, and genotype for two drugs that carry a high risk of adverse events with overexposure.

In conclusion, a PBPK modeling approach was used to explore dosing considerations for fentanyl and methadone in children with obesity. Model simulations for fentanyl confirm previous findings of differences in clearance with obesity and highlight the importance of considering both age and obesity status when selecting the infusion rate that is most likely to achieve C_{ss} values within the target range. Methadone dosing simulations highlight the importance of considering the *CYP2B6* genotype for dosing when possible and show that *CYP2B6*6/*6* children with obesity are at greatest risk of overexposure relative to wildtype children without obesity. This PBPK modeling approach can be applied to explore the dosing of other important drugs in children with obesity.

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Methadone pharmacokinetic data were accessed through the Eunice Kennedy Shriver NICHD Data and Specimen Hub (DASH; https://dash.nichd.nih.gov/). To help expand the knowledge base for pediatric medicine, the PTN is pleased to share data from its completed and published studies with interested investigators. For requests, please contact: ptn-program-manager@dm.duke.edu.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

J.G.G., F.O.C., J.L.F., A.N.E., E.M.P., K.M.W., W.J.M., A.M.A., A.A.-U., P.D., and D.G. performed the research and wrote the manuscript. J.G.G., F.O.C., A.N.E., and D.G. designed the research. J.G.G. and F.O.C. analyzed the data.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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