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Drug Dose Selection in Pediatric Obesity: Available Information for the Most Commonly Prescribed Drugs to Children

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Abstract

Obesity rates continue to rise in children, and little guidance exists regarding the need for adjustment away from total body weight-based doses for those prescribing drugs to this population of children. A majority of drugs prescribed to children with obesity result in either sub-therapeutic or supra-therapeutic concentrations, placing these children at risk for treatment failure and drug toxicities. In this review, we highlight available obesity-specific pharmacokinetic and dosing information for the most frequently prescribed drugs to children in the inpatient and outpatient clinical settings. We also comment on available dosing recommendations for drugs prescribed to treat common pediatric obesity-related comorbidities. This review highlights that there is no safe or proven 'rule of thumb,' for dosing drugs for children with obesity, and a striking lack of pharmacokinetic data to support the creation of dosing guidelines for children with obesity for the most commonly prescribed drugs. It is important that those prescribing for children with obesity are aware of these gaps in knowledge and of potential drug treatment failure or adverse events related to drug toxicity as a result of these knowledge gaps. Until more data are available, we recommend close monitoring of drug response and adverse events in children with obesity receiving commonly prescribed drugs.

1 Background

The World Health Organization (WHO) declared childhood obesity one of the most serious global health problems of the 21st century, with an estimated 124 million children with obesity worldwide [1]. Obesity, as defined by the Centers for Disease Control (CDC), encompasses any child with a body mass index (BMI, kg/m^2) of or greater than the 95th percentile for their age and sex [2]. In the United States (US), one in five children between the ages of 2–19 years meets BMI criteria for obesity [3]. In addition to common pediatric illnesses (e.g., otitis media, asthma, fever), these children also experience obesity-associated co-morbidities (e.g., hypercholesterolemia, hypertension, type 2 diabetes mellitus) that

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frequently require prescription drugs to control or cure symptoms [4]. However, optimal drug dose selection remains unclear for children with obesity [5, 6].

Drug dose selection in pediatrics is typically based on total body weight (TBW), with dosing recommendations derived from pharmacokinetic data in healthy adults or children. Sometimes allometric scaling is used to scale down drug doses from adult recommendations to children, who are generally smaller in size. However, this method is flawed for children with obesity, whose TBW may equal or even exceed that of an adult, while their organ anatomy and physiology remain developmentally immature and distinctly different from an adult [7–10]. Thus, neither TBW nor allometric scaling may adequately describe best dosing practices for children with obesity, despite frequent use of both strategies [7]. Additionally, in order to achieve the desired therapeutic effect (i.e., pharmacodynamics), the 'best' drug dose selection strategy must also account for potential variability in disease phenotype between children with and without obesity (e.g., asthma, discussed later in this manuscript) [11].

Upon recent review, approximately two-thirds of the drugs prescribed to children with obesity resulted in either sub-therapeutic or supra-therapeutic concentrations, placing these children at risk for treatment failure and drug toxicities [5]. Subsequently, drug dose individualization in obesity has appropriately received increased attention in the last decade [5–8, 10, 12–15]. However, agents prioritized for study have primarily focused on drugs with a narrow therapeutic index and high risk of serious toxicity, leaving a critical information gap for some of the most commonly utilized drugs in pediatrics. In this review, we highlight available obesity-specific pharmacokinetic, pharmacodynamic, and dosing information for the most frequently prescribed medications to children in the inpatient and outpatient clinical setting. We also comment on available dosing recommendations for common pediatric obesity-related comorbidities and discuss the lessons to be learned from the data available, identifying areas of focus for future research.

2 Search Strategy

To identify the most commonly prescribed drugs in the pediatric inpatient setting, we used the Pediatric Health Information System (PHIS), a nationally representative database of clinical/resource utilization data from over 45 pediatric hospitals in the US, to generate a list of the most frequently prescribed drugs in a single year (2017). This list was cross-referenced with medications identified as commonly prescribed in the pediatric hospital setting in a recent publication by Callaghan, to ensure inclusion of commonly prescribed drugs with known pharmacokinetic data available for review [7]. Outpatient drugs were selected from a publication of the most commonly prescribed outpatient drugs to children (2002–2010) by Chai et al. [16], which used two large outpatient prescription databases and, to our knowledge, represents the most complete outpatient drug list available to date. Intravenous (IV) fluids (e.g., normal saline, dextrose in water) and topical formulations (e.g., mupirocin, triamcinolone) were considered outside the scope of this review and were specifically excluded. Following removal of these formulations from the originally compiled inpatient and outpatient drug lists, the literature review ultimately included 22 inpatient (Table 1) and 15 outpatient drugs (Table 2).

Once the lists of commonly prescribed inpatient (Table 1) and outpatient (Table 2) drugs were compiled, applicable articles were identified using PubMed MeSH term-based searches including the key words (1) weight, body size, and obesity, (2) pediatrics, children, or adolescents, and (3) generic and trade names for each drug included in Tables 1 and 2. Additionally, we expanded this search to include studies of drugs used specifically to treat obesity co-morbidities (e.g., hypercholesterolemia, hypertension, insulin resistance, etc.). Although these drugs (Table 3) may be less frequently prescribed to children in general, they are more likely to be prescribed to children with obesity specifically, and thus were deemed pertinent to include in this review.

3 Approaches to Drug Dose Selection

The lack of pharmacokinetic clinical trials for drug dose selection in children with obesity makes generalization of dosing recommendations difficult [6]. In general, two dosing strategies have been proposed for children with obesity: allometric scaling and physiologically-based dosing.

3.1 Anthropometrics-Based Dosing and Allometric Scaling

Allometric scaling refers to dosing based on body size scaled to a fixed exponent [8]. This exponent can be 1 (which defines a linear relationship between dose and body size), 0.75 (Klieber's Law, commonly utilized in biology) or any other numerical value [17]. Recently, a scaling exponent specific to obesity based on the theory-based size descriptor of normal fat mass has been proposed by Anderson and Holford [8]. However, it remains unclear which anthropometric measure of size is most appropriate for scaling. Body weight, volume, and surface area have all been proposed.

TBW-based dosing is the most commonly utilized and appears to be appropriate for some drugs, but not others [5]. Differences are noted even within a given drug class (e.g., antimicrobials). For example, TBW-based dosing appears appropriate for clindamycin, vancomycin, cefazolin, and ceftriaxone [18], but leads to overdose and adverse events for gentamicin [7], azithromycin [19], and voriconazole [20]. To circumvent this variability in TBW-based dosing, some have proposed dosing based on the physiochemical properties of the drug. This approach assumes that a drug with high lipophilicity will have a larger volume of distribution (Vd) in obesity, requiring higher initial drug doses to achieve desired concentrations systemically and/or in the target organ. However, dosing is complicated by the potential for drug sequestering in, and unpredictable release from, adipose tissue, which may explain why, to date, no predictable, systematic relationship between the degree of drug lipophilicity and drug distribution has been identified [6, 10, 21]. For hydrophilic drugs, this pharmacokinetic relationship is even less clear [21].

Alternative anthropometric measures proposed for drug dose selection in obesity include BMI, body surface area (BSA), ideal body weight (IBW), and lean body weight (LBW), among others [14, 15]. Each of these indices of body composition comprises a calculation that incorporates a height component, which may be problematic, as obesity and its associated comorbidities (e.g., type 2 diabetes mellitus) can impact normal pediatric growth and development, including linear growth.

Historically, it has been noted that children with obesity/overweight tend to be taller than their normal-weight peers [22]. However, this trend does not continue into adulthood. Several studies note that children with obesity/overweight experience accelerated linear growth in childhood [23] and/or puberty [24, 25], followed by decreased height gain [23] that results in terminal height below [26] or equal to [23–25] peers without obesity. This altered pattern of linear growth affects BMI, BSA, IBW, and LBW calculations; therefore, some have proposed developing nomographs specific for children with obesity to aid drug dose selection [7]. We are currently exploring the utility of obesity-specific growth curves for dosing recommendations of metformin.

Obesity-associated alterations in organ size may also play a role in drug dose selection, particularly for pharmacologic agents that undergo biotransformation or metabolism in those organs. Liver volumes, for example, positively correlate with BSA [27], which is higher in obesity. Theoretically, larger liver volumes could alter the capacity for hepatic drug clearance and/or hepatic blood flow; however, the impact of intra-organ fat infiltration on these relationships has not been assessed in children with obesity.

Overall, the lack of evidence for dosing drugs based on TBW or other anthropometric measures for the vast majority of drugs prescribed to children with obesity makes generalization of dosing recommendations difficult [6], and it is likely that no single size measure is appropriate for all drugs [18]. Physiologically-based dosing, an alternative dosing approach increasingly recognized by regulatory agencies, focuses on organ function rather than size to help guide drug dose selection.

3.2 Physiologically-Based Dosing

An evolving approach to drug dose selection in obesity is based on the physiological changes that accompany obesity, and how these changes may impact drug absorption, distribution, metabolism, and excretion [10] (Fig. 1). For example, drug bioavailability may be altered due to differences in gastric emptying time, blood flow, drug transport, drug metabolizing enzyme expression and/or activity in individuals with versus those without obesity.

Specifically, obesity is associated with increased lean and total body mass, but decreased lean-to-total body mass ratio [12]; increased blood volume, cardiac output, splanchnic and hepatic blood flow [28]; and altered drug-binding protein concentrations for some drugs (e.g., propranolol and α_1 acid glycoprotein) [29], but not others (e.g., phenytoin and albumin) [12, 29]. Combined, these obesity-related perturbations in physiology may account for the large amount of variability observed in the V_d for a given drug in obese individuals [6, 21, 28], unaccounted for by body size alone. Additionally, obesity-related hypertrophy of metabolically active organs (e.g., liver, kidneys) [6, 30], and subsequent alterations in blood flow to and from these organs [28], can also affect total drug clearance, as demonstrated by studies of the renally cleared drug vancomycin [31] and the hepatically cleared drug carbamazepine [32, 33]. Furthermore, individuals with obesity frequently have hepatic fat infiltration, a condition called non-alcoholic fatty liver disease, which can be associated with inflammation [34]. Inflammation, in turn, can affect hepatic metabolic activity, including drug metabolizing enzymes in the cytochrome P450 family (CYPs) [21]. Available studies to

date suggest that activity of some hepatic CYPs appears increased in individuals with obesity (e.g., CYP2E1, CYP2D6), while the activity of others (e.g., CYP3A4, CYP2C19) appears decreased [35].

With the complex interplay of the many physiologic consequences of obesity, comprehensive, computer-based frameworks capable of synthesizing the available obesity physiology knowledge to study the pharmacokinetics and pharmacodynamics of drugs in obesity have gained popularity. These physiologically-based pharmacokinetic and pharmacodynamic models (PBPK-PD) show promise in pediatrics [36], but depend on the quality of the physiologic data available for obese children, which are often sparse [5]. Pharmacologic knowledge for children with obesity is urgently needed to provide optimal drug dosing recommendations, particularly for the most commonly prescribed drugs for children and for children with obesity in the inpatient and outpatient setting.

4 Summary of Data Available for Commonly Prescribed Inpatient Drugs

The number of studies examining pharmacokinetic data for drugs in children is growing, particularly for those drugs most commonly prescribed in the inpatient hospital setting. Areas of progress and focus include anesthetics and antimicrobials, with some studies specifically examining differences in drug metabolism in children with versus without obesity. The motivation for prioritizing these two drug classes for investigation likely stems from their narrow therapeutic index and the heightened risk of complications, adverse outcomes, or therapeutic failures if adequate systemic drug concentrations are not achieved [37]. Still, for the majority of the most frequently prescribed drugs to children during hospitalization (Table 1), data are severely lacking.

4.1 Anesthetics

Of the most commonly prescribed anesthetics, pharmacokinetic studies in children with obesity were identified for the following drugs: propofol [38–41], fentanyl [42–44], midazolam [42, 45, 46], and morphine [42]. Adult obesity data also exist for these drugs. Combined, these studies demonstrate significant alterations in the pharmacokinetics of anesthetics necessitating modifications to the routinely employed TBW-based drug dosing strategies. The recommendations in exactly how to alter dosing for patients with obesity varies by drug and from study to study. Of note, some studies included pharmacokinetic data for loading doses of the drug, and others for maintenance dosing; we chose to include information on both types of studies, as both types of dosing can be affected by obesity and would therefore affect drug dosing recommendations. We will clarify which studies were of induction dosing only throughout this section.

4.1.1 Propofol—The data for propofol in obese children are mixed. Diepstraten et al. proposed that an individual's TBW is the most significant determinant of drug clearance, advocating that children with obesity receive TBW-based dosing to achieve maintenance anesthesia [39]. However, Olutoye et al. reported that children with obesity require a lower weight-based dose for anesthesia induction than healthy-weight children [40]. Adult literature report similarly mixed findings, with some reporting TBW-based dosing to be best

[47], and others suggesting LBW [48] as a better metric to achieve adequate target anesthesia goals with propofol.

4.1.2 Fentanyl—Studies comparing fentanyl infusion in pediatric patients with obesity undergoing bariatric surgery found Vd values comparable to previously published studies in children without obesity, but increased drug clearance, likely secondary to increased hepatic blood circulation [43]. Based on these findings, a dosing strategy based on IBW or LBW, rather than TBW, is proposed for children with obesity, in line with recommendations from the adult bariatric surgery literature [43, 49]. One study in adults, by Shibutani et al., confirms that TBW-based dosing of fentanyl may result in overdose [50].

4.1.3 Midazolam—Studies of midazolam pharmacokinetics in children with obesity identify a marked increase in peripheral Vd, indicating a potential need for higher initial drug dose administration for continuous infusion, in order to achieve therapeutic exposures [45]. A study by van Rongen et al. describes higher observed clearance of midazolam in children with obesity compared with adults with obesity [45]. The authors propose that this observation may be due to decreased CYP3A activity in adults versus children and highlight the fact that extrapolation of adult obesity pharmacokinetic data to children can be fraught with problems [46].

4.1.4 Rocuronium—Although no pediatric data are available, adult data for rocuronium, a commonly prescribed muscle relaxant/paralytic during anesthesia, suggest the duration of action of rocuronium is prolonged in patients with obesity when prescribed according to their TBW [51]. Another study showed a shorter duration of action without prolonging onset time or complicating conditions necessary for successful intubation [52]. These studies suggest dosing of rocuronium should be based on a patient's IBW for adults with obesity [51, 52].

4.2 Antimicrobials

Consequent to body weight being identified as a predictor of antibiotic treatment failure [53], antimicrobials have been another drug class of focus for pharmacokinetic studies in children with obesity. In the inpatient setting, the most robust information exists for vancomycin [54–60], one of the drugs identified as most commonly prescribed in the inpatient setting. We also identified two pediatric studies of cefazolin [61, 62] and one of clindamycin in obesity [63]. No studies of ceftriaxone were found.

4.2.1 Vancomycin—Studies of vancomycin pharmacokinetics in children with obesity reveal mixed results, which appear to bear no clinical significance for children with versus those without obesity [54–57, 59]. There do not appear to be major differences in vancomycin clearance or Vd; although a few studies have identified differences in vancomycin troughs of questionable clinical significance between children with versus those without obesity [54, 59]. Heble et al. observed patients with obesity were more likely to experience higher initial trough concentrations when dosed based on TBW (median 14.4 μg/mL vs 10.5 μg/mL; $p < 0.001$), though all troughs were within a normal therapeutic range [54]. Madigan et al. used a higher daily dose of vancomycin to attempt to achieve goal

trough concentrations in patients of all weight categories and found that adolescents with higher weights were more likely to experience elevated trough concentrations compared with all other groups of children [59]. Interpretation of these results was confounded by age, as significant differences in troughs were also observed based on age alone (i.e., adolescent vs child) [59]. Moffett et al. found a trend toward patients with obesity experiencing higher trough concentrations, but the differences between groups were not statistically or clinically significant [55]. Three additional studies found no evidence of differences in vancomycin pharmacokinetics between children with versus those without obesity [56–58]. Given the lack of clinical relevance of the sometimes statistically significant changes in vancomycin pharmacokinetics in children with obesity, some studies recommend dosing based on TBW for all pediatric patients, regardless of weight status [55].

4.2.2 Cefazolin—Cefazolin is a drug frequently prescribed in the hospital setting, especially peri-operatively. We identified two small studies examining cefazolin pharmacokinetics in pediatric patients with obesity [61, 62]. Cefazolin has hydrophilic properties; however, drug lipophilicity was not predictive of drug distribution within tissues and the studies found no differences in cefazolin clearance or Vd, adjusted for TBW, in children with versus those without obesity [61, 62]. Based on these limited data, it is recommended that cefazolin dosing be based on TBW for all patients, regardless of weight status (e.g., 30 mg/kg for perioperative prophylaxis [64]); however, the maximum safe total dose remains unknown. Maximum doses of both 2 g and 3 g have been proposed, based on studies in adults [62].

4.2.3 Clindamycin—Hypothesizing that clindamycin may require dose adjustment for patients with obesity due to the drug's lipophilic properties, Smith et al. examined pharmacokinetic differences in children with and without obesity [63]. Similar to cefazolin, lipophilicity was not predictive of clindamycin pharmacokinetics, and TBW-based dosing was recommended for children of all weight statuses.

4.3 Other Commonly Prescribed Inpatient Drugs

4.3.1 Acetaminophen—In addition to its frequent over-the-counter use in the outpatient setting, we identified acetaminophen as the number one prescribed drug in the inpatient setting. Despite its frequent use, only one study of acetaminophen pharmacokinetics in children with obesity and non-alcoholic fatty liver disease (NAFLD) was identified [65]. Although this study did not find significant differences in circulating acetaminophen concentrations after a 5-mg/kg (up to 325 mg) single oral dose administration, it did identify significantly higher concentrations of the acetaminophen glucuronide metabolite in the plasma and urine of children with NAFLD, suggesting that hepatic glucuronosyltransferase (UGT) activity is upregulated in the presence of hepatic fat. This observation of increased UGT-mediated acetaminophen metabolism in obesity is supported by several adult studies [66–68]. Van Rongen et al. found that adults with obesity had significantly lower concentrations of acetaminophen after IV dose administration, putting them at risk for therapeutic failure; however, they also had higher concentrations of hepatotoxic CYP2E1-mediated acetaminophen metabolites, cysteine and mercapturate, putting them at higher risk for toxicity [67]. Thus, despite the potential need for higher initial doses of acetaminophen

due to increased UGT activity, individuals with obesity may not tolerate the higher doses required, due to increased CYP2E1 activity leading to overproduction of hepatotoxic acetaminophen metabolites.

4.3.2 Other Inpatient Drugs—The data for other commonly prescribed pediatric inpatient drugs are even more sparse, with respect to pharmacokinetic investigations in children with obesity. No published information could be found for ondansetron, ibuprofen, diphenhydramine, ketorolac, ranitidine, oxycodone, ceftriaxone, hydromorphone, lorazepam, and methylprednisolone. For some of these drugs, data were available for adult patients with obesity; however, we have already highlighted the potential pitfalls in extrapolating pharmacokinetic data from adults with obesity to children (e.g., midazolam and CYP3A4) [46, 69].

5 Summary of Data Available for Commonly Prescribed Outpatient Drugs

Despite the frequency and the abundance of drugs prescribed to children in the outpatient setting [16] (Table 2), minimal information is available for drug dose recommendations for children with obesity. Specifically, we found no pharmacokinetic data to support evidenced-based drug dosing in children with obesity for the most frequently prescribed outpatient drugs: amoxicillin, amoxicillin-clavulanate, cefdinir, cephalexin, prednisolone, ibuprofen, trimethoprim/sulfamethoxazole, hydrocodone/acetaminophen, methylphenidate, dextromethorphan/phenylephrine/chlorpheniramine, prednisone, or amphetamine/dextromethorphan. Several studies of these agents were identified for adults with obesity (e.g., steroids [69–71]). Studies of oral steroids reported poor oral absorption and increased apparent drug clearance for subjects with obesity, leading to overall decreased efficacy [71]. Interestingly, one study by Milsap et al. pointed out that the relative baseline hypercortisolemia observed in patients with obesity may explain these observations of diminished drug response to exogenous steroids in obesity [70]. This hypothesis is also supported by evidence of attenuated cortisol responsiveness for the inhaled steroid budesonide in adults with obesity [72].

We did identify a single study on the pharmacokinetics of IV azithromycin in children with community-acquired pneumonia [19]. Although the study suggests that increased weight is associated with decreased clearance, it does not specifically comment on the obesity status of subjects in the patient demographics. We also identified a single study of montelukast pharmacodynamics for children with asthma, comparing patient outcomes using the Asthma Control Test for children with and without comorbid obesity [73]. Interestingly, patients with obesity had a significantly better response to a 24-week treatment course of montelukast than peers without obesity [73]. The authors propose that the leptin-induced leukotriene activation associated with obesity provides more asthma drug targets for montelukast, a leukotriene inhibitor. The results of a large pediatric clinical trial (>2500 children) published by McGarry et al. also provide supporting evidence that children with obesity benefit from montelukast for asthma control, suggesting that perhaps asthma phenotypes differ between children with versus those without obesity [74].

5.1 Asthma Inhalants

We identified compelling evidence that standard doses of inhaled asthma control medications are insufficient for children with obesity (e.g., poorer symptom control and pulmonary function testing scores) [74–76]. However, we could not find any published dosing studies of asthma inhalants used in children with obesity. In one of the largest pediatric clinical trials, involving over 1000 children with obesity and nearly 2000 children without obesity, asthma responsiveness to standard single-dose inhaled albuterol was inferior for children with versus those without obesity, as assessed by both objective (i.e., spirometry) and subjective (i.e., symptom relief) asthma metrics [74]. In this study, children with obesity were also more likely to need inhaled corticosteroids with long-acting β2 agonists (e.g., fluticasone/salmeterol) for asthma control [74]. However, a large retrospective analysis of four longitudinal adult trials concluded that individuals with overweight/obesity required longer to achieve peak spirometry on fluticasone/salmeterol treatment [75]. In another retrospective longitudinal study analysis of inhaled fluticasone alone or in combination with a steroid, adults with morbid obesity were at twofold greater risk for asthma exacerbation during treatment (39%) than all other BMI groups ($n = 682$) [76]. One commonly proposed mechanism for this observed therapeutic failure from standard inhaled drug doses in obesity is the increased inflammatory burden secondary to obesity, compounded by the already existing asthma-associated inflammation [74, 77]. We could not find pharmacokinetic or pediatric data to support these observations of altered pharmacodynamics in individuals with obesity and asthma.

6 Other Drugs Commonly Prescribed for Obesity Co-Morbid Conditions

Asthma is not the only chronic medical condition that disproportionately affects patients with obesity [4]. Other common obesity-comorbid conditions requiring prescription drug therapy include hypercholesterolemia, hypertension, insulin resistance, and gastroesophageal reflux disease [78]. In this section, we review the pharmacokinetics and dosing information available for the pharmacologic agents frequently used to treat these pediatric comorbid conditions (Table 3).

6.1 Statins

Similar to adults, childhood obesity is accompanied by hypercholesterolemia, a risk factor for developing cardiovascular disease later in life [79]. Statins, substrates for hepatic transporter *SLCO1B1*, are considered first-line pharmacotherapy for this condition in children as young as 8 years [80]. Pediatric [81, 82] and adult [83, 84] studies confirm that, within the statins drug class, the degree of drug lipophilicity alone fails to predict systemic drug exposure with respect to patient BMI. Recently, a *SLCO1B1* genotype-stratified pharmacokinetic study of fixed-dose pravastatin demonstrated a weak positive correlation between systemic drug exposure and BMI *Z*-score in children [81]. However, in a subset of children with the wild-type *SLCO1B1* genotype (c.521TT) and BMI *Z*-score >2.5 ($n = 4$), systemic pravastatin exposures were two- to fivefold in excess of all other children with the same genotype, suggesting that there may be differences in hepatic uptake of pravastatin in children with versus those without obesity [81, 82].

6.2 Anti-Hypertensives

Despite a known predominance of hypertension in patients with obesity, knowledge gaps remain with regard to appropriate drug dose selection of anti-hypertensives for patients with obesity. In a study of calcium channel blockers, where children with (n = 16) and without obesity (n = 17) were given identical mg/m^2 drug doses, children with obesity demonstrated attenuated blood pressure response [85]. This observation is echoed in adult studies where findings of blunted blood pressure response to calcium channel blockers are thought to be secondary to higher drug Vd in the peripheral compartment in patients with obesity [86].

A trend towards higher Vd in patients with obesity was also observed for β-blockers, especially those with higher lipophilicity (e.g., propranolol, metoprolol) [21]. However, when Vd was corrected for TBW, the difference in Vd between obese and non-obese individuals diminished by approximately 15–35% [21]. Collectively, these observations highlight that dosing based solely on drug lipophilicity is inappropriate for β-blockers and suggest that these drugs preferentially bind to lean tissue. To our knowledge, studies of dosing based on LBW or IBW are lacking for β-blockers.

We were unable to identify any pharmacokinetic studies for angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) in obesity. A small pharmacodynamic study by Hanafy et al. observed no differences in therapeutic response to these agents in children with (n = 3) versus without obesity (n = 3) [85]. Overall, the lack of robust data, beyond a handful of small pharmacokinetic studies of anti-hypertensives in children with obesity, preclude firm dosing recommendations in this emerging patient population.

6.3 Proton Pump Inhibitors

Children with obesity are six times more likely than peers without obesity to have gastroesophageal reflux disease (GERD) [87], a chronic condition for which proton pump inhibitors (PPIs), potent acid suppressive medications, have become the mainstay of therapy [88]. Availability of pharmacokinetic PPI data in obesity is very limited, with published pediatric data focused on the PPI pantoprazole. In two independent prospective investigations, Shakhnovich et al. have demonstrated decreased apparent drug clearance for pantoprazole in obesity [89–91], advocating for LBW-based dosing [89, 90] and avoidance of empiric dose escalation [91] previously proposed in an adult study [92]. Given the growing concerns regarding association of PPI exposure with adverse events in children (e.g., infections, osteopenia) [93], to avoid unnecessary systemic PPI overexposure, studies are needed to investigate whether the decrease in CYP2C19-mediated apparent clearance for pantoprazole is a class effect for all PPIs in obesity.

6.4 Metformin

Metformin is approved for treating children with type 2 diabetes mellitus. It is also prescribed off-label for obesity and/or insulin resistance, as well as comorbidities such as NAFLD, polycystic ovary syndrome, and premature pubarche. Despite its wide use, pharmacokinetic studies of metformin for children with obesity are limited to one published

abstract in children with type 2 diabetes mellitus [94] and two studies in children with obesity and insulin resistance [95, 96].

In pediatrics, metformin is typically prescribed as a fixed total daily dose of 2000 mg, regardless of patient weight; however, evidence is emerging that children with obesity may require higher drug doses to achieve systemic exposures comparable to non-obese peers. In a pharmacokinetic study of metformin concentrations over time for children with insulin resistance, drug clearance increased with TBW and LBW, both of which are higher in children with versus without obesity [96]. As a consequence of this increased clearance, lower systemic exposure to metformin was observed in children with obesity, risking therapeutic failure in this patient population unless drug doses are adjusted [96]. The authors hypothesized that the observed alterations in drug clearance may be secondary to obesity-related changes in kidney function, although differences in drug absorption and/or bioavailability in obesity offer an alternative explanation. A study of metformin in adult patients with type 2 diabetes mellitus supports the renal hypothesis [97]. In this study by Bardin et al., obesity and TBW did not affect metformin absorption rate, while Vd and clearance correlated positively with LBW, which is thought to be related to glomerular filtration rate and kidney function [97].

Metformin is primarily cleared by the kidneys, where it is actively secreted by renal transporters OCT2, and MATE-1/MATE-2K [98]. While metformin is not actively cleared in the liver, it serves as a substrate for the hepatic uptake transporter OCT1, the expression of which significantly correlates with BMI and percent fat mass [95]. Therefore, co-administration of metformin with other drug substrates for hepatic OCT1 (e.g., cimetidine, tramadol) to children with obesity can lead to unforeseen alterations in the pharmacokinetics and pharmacodynamics of all the pharmacologic agents administered [95].

7 Discussion

The amount of literature available regarding the pharmacokinetics and pharmacodynamics of drugs prescribed to children with obesity is growing; however, it focuses primarily on drugs with a narrow therapeutic index and a high risk of toxicity (e.g., chemotherapeutics, analgesics, and sedatives used intra-operatively, or in emergency/intensive care settings) [6, 15, 37]. While prioritization of such agents is unequivocally important, it leaves a critical information gap for the drugs most commonly prescribed to children in the inpatient and outpatient settings, including drugs specifically prescribed to treat obesity and its many comorbidities (e.g., hypercholesterolemia, hypertension, etc.). This lack of data currently impacts 124 million children with obesity worldwide [1].

More pharmacologic information is available for drugs used in the inpatient, compared with the outpatient, clinical setting. The most abundant pediatric data were identified for antibiotics; however, no information was available for antibiotics most commonly prescribed in the outpatient setting (e.g., amoxicillin, cefdinir, trimethoprim/sulfamethoxazole, etc.). Although some data were available for approximately 50% of the anesthetics/analgesics/sedatives used in the inpatient setting, no pediatric data were available for the commonly utilized steroids (dexamethasone and methylprednisolone; Table 1). No pediatric data were

available for any of the analgesics or steroids prescribed in the outpatient setting, nor was any information available for drugs commonly prescribed to children for attention deficit hyperactivity disorder (Table 2).

The available information for oral and inhaled pharmacologic agents used in both the inpatient and outpatient setting to treat asthma, a common pediatric condition, suggests that montelukast is a beneficial primary and/or adjunct treatment option in obesity and that standard doses of all other agents appear inadequate for patients with obesity [73]. Surprisingly, no follow-up dose escalation studies were identified, despite available studies indicating the need for dose escalation in obesity [74]. Limited information was available for other comorbidities that disproportionately affect children with obesity (e.g., hypercholesterolemia, hypertension, insulin resistance, type 2 diabetes mellitus, GERD), but a common theme that adjustments to standard dosing are warranted for some drugs (e.g., metformin) but not others (e.g., pantoprazole) emerged (Table 3). Furthermore, when dose adjustments are warranted, dose escalation is not always the answer. For example, due to the decreased apparent clearance (L/h/kg TBW) of pantoprazole in obesity, children with obesity achieved higher systemic exposures for every mg/kg TBW drug received, placing them at risk for PPI-associated toxicities (e.g., infection, osteopenia) [82, 89–91].

Similarly, TBW-based dosing is not always the appropriate answer. Although at first glance, Table 1 may suggest that TBW is appropriate for dosing antibiotics for children with obesity, this observation cannot be extrapolated to all antibiotics. While the few studies we identified for these commonly prescribed antibiotics suggested TBW-based dosing may be appropriate, several of them lack robust pharmacokinetic evidence for children with obesity. Additionally, we found some evidence that TBW-based dosing is inappropriate for children with obesity receiving other antibiotics, like gentamicin [7] or azithromycin [19].

8 Conclusion

Overall, this review of the literature highlights that there is no safe or proven ‘rule of thumb,’ for dosing medications for children with obesity. Drug pharmacokinetics, pharmacodynamics, and dosing recommendations should be investigated in this patient population and will likely reflect an interplay between drug physiochemical properties, body size, and the impact of obesity on human physiology, rather than any one of these determinants alone. Currently, it is important that those prescribing for children with obesity are aware of these gaps in knowledge and are cognizant of potential drug treatment failure as a result of inadequate target organ/tissue exposure, or adverse events related to drug toxicity and systemic overexposure. Until more data are available, we recommend close monitoring of drug response and adverse events in children with obesity, and consideration of dose escalation for inhaled asthma agents.

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Key Points

This review highlights that there is no safe or proven ‘rule of thumb’ for dosing drugs for children with obesity.

It is important that those prescribing for children with obesity are aware of these gaps in knowledge and of potential drug treatment failure or adverse events related to drug toxicity as a result of these knowledge gaps.

Until more data are available, we recommend close monitoring of drug response and adverse events in children with obesity receiving commonly prescribed drugs; empiric dose escalation for asthma inhalants may be warranted.

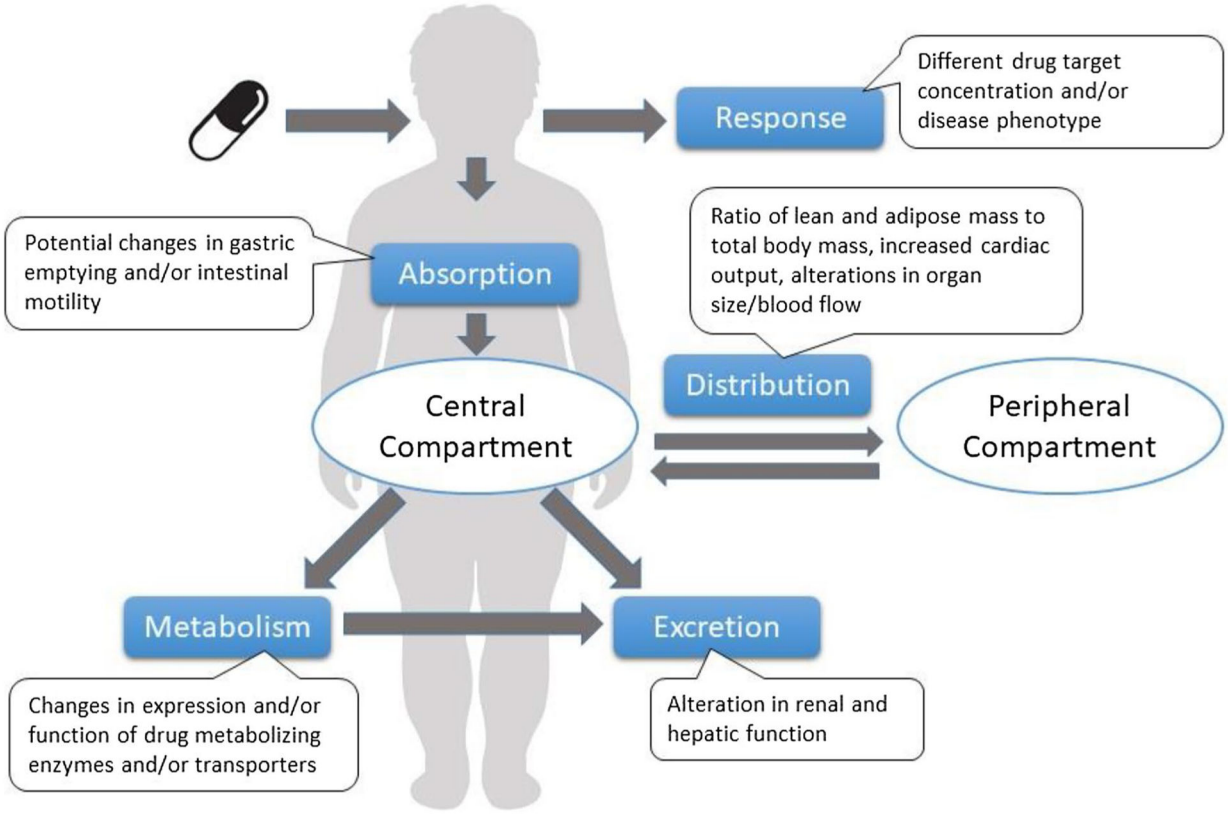

Fig. 1.
Effects of obesity on drug absorption, distribution, metabolism, and excretion

Table 1

Most frequently prescribed pediatric inpatient drugs

Category	Drug	Summary of evidence
Antimicrobials	Cefazolin	No difference in CL or Vd [14, 61]. Dose based on TBW
	Ceftriaxone	No specific studies identified; TBW suggested for cephalosporins as a drug class [7]
	Vancomycin	No clear difference in CL or Vd. Patients with obesity may be more likely to experience higher trough concentrations, but this is of uncertain clinical significance. Most recommend dosing based on TBW [14]
	Clindamycin	No clear difference in pharmacokinetic properties. Dose based on TBW [63]
Analgesics/ anesthetics	Acetaminophen	Obesity may result in decreased drug exposure, but changes in CYP2E1 metabolic pathways preclude any necessary dose adjustments [67]
	Propofol	Mixed results regarding safest dosing; some suggest TBW-based for maintenance dosing [38] and other LBW for induction dosing to achieve desired exposure [40]
	Fentanyl	Increased drug clearance in adolescents with obesity compared with adults. Some studies recommend dosing based on IBW [43] or other adjusted body weight [50]
	Morphine sulfate	IBW has been suggested for dosing in children with obesity [7, 42]
	Rocuronium	No pediatric studies identified. Adult studies suggest dosing based on IBW [51, 52]
	Ibuprofen	No specific studies identified
	Ketorolac	No specific studies identified
	Oxycodone	No specific studies identified
	Hydromorphone	No specific studies identified
Benzodiazepines	Midazolam	Increased peripheral Vd, necessitating possible higher initial doses to achieve desired exposure [45]
	Lorazepam	No specific studies identified
Steroids	Dexamethasone	No specific studies identified
	Methylprednisolone	No specific studies identified
Inhaled drugs	Albuterol	Increased likelihood of therapeutic failure using standard dosing (OR 1.24–1.38; 95% CI 1.03–1.7); dose escalation studies warranted [74]
	Fluticasone	Increased likelihood of therapeutic failure using standard dosing in adults (twofold increase in morbidly obese adults compared with all other adults) [72]
Other drugs	Ondansetron	No specific studies identified
	Diphenhydramine	No specific studies identified
	Enoxaparin	Some studies noted higher doses needed to reach therapeutic concentrations for VTE prophylaxis in patients with obesity. However, dose based on TBW; treat to target (anti-Xa 0.1–0.3 IU/mL) [7]
	Ranitidine	No specific studies identified

CI confidence interval, *CL* clearance, *IBW* ideal body weight, *LBW* lean body weight, *OR* odds ratio, *TBW* total body weight, *Vd* volume of distribution, reported in units per kg TBW

Table 2

Most frequently prescribed pediatric outpatient drugs [16]

Category	Drug	Summary of evidence
Antimicrobials	Amoxicillin	No specific studies identified
	Azithromycin	No specific studies identified
	Cefdinir	No specific studies identified
	Cephalexin	No specific studies identified
	Trimethoprim/sulfamethoxazole	No specific studies identified
Analgesics	Ibuprofen	No specific studies identified. Study in adults suggests increased Vd and CL in obesity [69]
	Hydrocodone/acetaminophen	No specific studies identified
ADHD drugs	Methylphenidate	No specific studies identified
	Dextromethorphan/phenylphrine/ chlorpheniramine	No specific studies identified
	Amphetamine/dextromethorphan	No specific studies identified
Steroids	Prednisolone	No specific studies identified. However, studies of steroids in adults revealed poor oral absorption and increased CL leading to poor efficacy [70]
	Prednisone	No specific studies identified
Asthma treatment	Montelukast	Greater improvement in asthma symptom scores in pts with obesity compared with healthy weight [73]
Inhaled drugs	Albuterol	Increased likelihood of therapeutic failure using standard dosing (OR 1.24–1.38; 95% CI 1.03–1.7); dose escalation studies warranted [74]
	Fluticasone	No specific studies identified. However, increased likelihood of therapeutic failure using standard dosing in adults (twofold increase in morbidly obese adults compared with all other adults) [72]

ADHD attention deficit hyperactivity disorder, *CI* confidence interval, *CL* clearance, *OR* odds ratio, *Vd* volume of distribution

Table 3

Drugs commonly prescribed for obesity co-morbid conditions

Condition	Drug/drug class	Summary of evidence
Diabetes mellitus/insulin insensitivity/obesity	Metformin	Increased clearance in patients with obesity, leading to lower systemic exposure; dose escalation may be warranted [96]
Hypertension	Calcium channel blockers	Single small study showed children with obesity may require higher doses to achieve optimal BP control [86]. No studies evaluating drug distribution in children with obesity
	β-Blockers	No specific studies identified. In adults, possible increased Vd in patients with obesity, especially in lipophilic drugs [21]. However, β-blockers preferentially bind lean body tissues, suggesting dosing based on lipophilicity of drugs alone is not adequate
	ACE inhibitors (ACEi) or angiotensin receptor blockers (ARBs)	No pharmacokinetic studies exist. Single study with very small sample size demonstrated no therapeutic difference for pts with obesity [85]
Gastroesophageal reflux disease	Proton pump inhibitors	Data only available for pantoprazole: LBW [89, 90] Decreased CL/F; thus, no empiric dose escalation warranted, if using fixed dosing [91]
	Histamine H2 receptor blockers (e.g., ranitidine)	No specific studies identified
Hypercholesterolemia	Statins	Few pediatric studies suggest correlation between BMI and drug exposure, but results are mixed [81, 82]

BMI body mass index, *CL/F* apparent total clearance of the drug from plasma, *LBW* lean body weight, *Vd* volume of distribution

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