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Pediatric Drug-Drug Interaction Evaluation: Drug, Patient Population, and Methodological Considerations

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Abstract

Hospitalized pediatric patients and those with complex or chronic conditions treated on an outpatient basis are commonly prescribed multiple drugs resulting in an increased risk for drug-drug interactions (DDIs). Although dedicated DDI evaluations are routinely performed in healthy adult volunteers during drug development, they are rarely performed in pediatric patients due to ethical, logistical, and methodological challenges. In the absence of pediatric DDI evaluations, adult DDI data are often extrapolated to pediatric patients. However, the magnitude of a DDI in pediatric patients may differ from adults because of age-dependent physiological changes that can impact drug disposition or response, and due to other factors related to the drug (e.g., dose, formulation) and the patient population (e.g., disease states, obesity). Therefore, the DDI magnitude needs to be assessed in children separately from adults, although a lack of clinical DDI data in pediatric populations makes this evaluation challenging. As a result, pediatric DDI assessment relies on the predictive performance of the pharmacometric approaches used, such as population and physiologically-based pharmacokinetic modeling. Therefore, careful consideration needs to be given to adequately account for the age-dependent physiological changes in these models to build a high confidence level for such untested DDI scenarios. This review article summarizes the key considerations related to the drug, patient population, and methodology, and how they can impact DDI evaluation in the pediatric population.

Keywords

pediatrics; drug-drug interactions; pharmacokinetics; pharmacodynamics

Potential Drug-Drug Interactions (DDIs) in Pediatric Patients

Drug-drug interactions (DDI) are a serious concern in pharmacotherapy whereby the pharmacological effect of a victim drug is either exaggerated or suppressed by the concomitant administration of a perpetrator drug. Depending upon the extent of DDI, the altered pharmacology may manifest as adverse effects, including both on- and off-

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target effects. Alternatively, suppression of a drug's pharmacological effect may lead to treatment failure. In some instances, a DDI can have a therapeutic benefit and has been deliberately accounted for in the recommended dosing regimen. The majority of the known therapeutically beneficial DDIs occur by pharmacodynamic (PD) interactions, such as synergistic effects of various combined antibiotic regimens and combined anesthetic-analgesic regimens in general anesthesia.[1,2] However, desired pharmacokinetic (PK) interactions can also be exploited to optimize a therapeutic regimen, such as ritonavir-boosted dosage of protease inhibitors in patients with human immunodeficiency virus (HIV).[3] Irrespective of the nature of a DDI (i.e., whether beneficial or detrimental), it is important to evaluate the DDI's magnitude in the target population where the interacting drugs are likely to be co-administered. Although DDI evaluations are routinely performed in healthy adult volunteers during drug development, limited studies have evaluated DDIs in pediatric patients due to ethical, logistical, and methodological challenges.[4] As a result, there are limited DDI data for most drugs used in pediatric patients, including the extent to which DDI magnitude varies with age. In the absence of DDI data that can inform dosing adjustments in pediatric patients, adult DDI data are extrapolated to pediatric patients without accounting for age-dependent physiological changes that can alter PK and PD.

Hospitalized pediatric patients often receive multiple drugs, resulting in a potential increased DDI risk. One retrospective cohort study evaluated the prevalence and characteristics of potential DDIs in hospitalized pediatric patients (<21 years of age) using the Pediatric Health Information System (PHIS) database, which included data from 43 freestanding children's hospitals.[5] The authors found that out of 498,956 hospitalizations in 2011, 49% were associated with ≥1 potential DDI. Also, they identified that in 41% of these hospitalizations, pediatric patients were exposed to a "major" potential DDI (defined as a DDI that is life-threatening or requires medical intervention to treat or prevent an adverse drug event). For infants, on day 1 of hospitalization, 21.8% were exposed to a potential DDI, increasing to 32% by day 30 of hospitalization. For pediatric patients >1 year of age, 34.7% and 66.3% were exposed to a potential DDI on day 1 and day 30 of hospitalization, respectively. Interestingly, the authors noted that half of the exposures were related to potential DDIs that were caused by less common drug pairs (≤3% of pediatric patients exposed per hospital day).

Another study that evaluated potential DDIs in pediatric intensive care unit (PICU) patients using the PHIS database found that, on average, patients were exposed to 10 distinct drugs during hospitalization and 20 drugs cumulatively during a hospitalization.[6] Out of 54,549 PICU patients <18 years of age, 75% were exposed to ≥1 potential DDI, and 69% were exposed to ≥1 "major" potential DDI. Potential DDIs were associated with specific diagnoses (neoplasms, circulatory systems, congenital anomalies, nervous system diseases), the presence of complex chronic conditions, increasing number of distinct drugs used, increasing PICU length of stay, and white race.[6]

Across both studies, several drug classes commonly involved in the potential DDIs were similar: opioids (25–29.7% of all potential DDIs), neurologic drugs (15–23.6%), anti-infective drugs (17–18.1%), renal diuretics (18.8%), and gastrointestinal drugs (10.5–13%).[5,6] In the study of PICU patients, additional drug classes noted included renal diuretics

(18.8%), analgesics and antipyretics (13.1%), psychotherapeutics (11.7%), and blood and coagulation drugs (10.4%).[6] Among the "major" potential DDIs, the top three drug pairs in both studies included fentanyl plus morphine, fentanyl plus midazolam, and midazolam plus morphine.[5,6] These DDIs can result in a potentially additive respiratory depressing effect.

Pediatric patients with complex or chronic conditions treated on an outpatient basis may also be at risk for potential DDIs.[7–10] Due to less monitoring by a health care professional, outpatients may be more susceptible to the adverse effects of DDIs. For example, a retrospective cohort study of Medicaid patients <18 years of age in Colorado reported that 35% of 242,230 patients received ≥2 concurrent drugs for at least one day.[7] The pediatric patients that received a greater number of concurrent drugs were at greater risk for potential DDIs and were exposed to less commonly prescribed drug classes (psychotropics, anticonvulsants, and opioids). Therefore, potential DDIs are common in hospitalized pediatric patients and patients with complex or chronic conditions treated on an outpatient basis. Additional studies are warranted to inform the DDI risk extent and guide therapeutic management when interacting drugs are co-administered.

Challenges with DDI Evaluation in the Pediatric Population

There are numerous ethical, logistical, and methodological challenges in evaluating DDI potential in pediatric patients, summarized in Table 1 and compared with adult DDI evaluation considerations. According to 21 CFR 50, subpart D, which describes clinical investigations in pediatric subjects associated with a more than minimal risk, there must be an anticipated benefit for children enrolled in clinical studies.[4,11] Therefore, DDI studies need to be performed in pediatric patients receiving the drug as part of their care.[4]

The analysis of DDI data from pediatric patients receiving the drugs per standard of care can present methodological challenges. Unlike DDI studies in healthy adult volunteers, analysis of DDI data from pediatric patients requires separating the effect of the DDI of interest from the confounding effects of disease states and other concomitant medications. Also, due to limitations around the collection of numerous PK samples (particularly in neonates and infants) and low informed consent rates, ensuring an adequate sample size across pediatric age groups to evaluate the DDI effect can be challenging.

A comprehensive literature review that searched articles published between 1945–2011 identified 145 reports of DDIs in pediatric patients ranging in age from birth to 20 years.[12] Seventy-four (49%) studies used a prospective design, 16 (11%) were retrospective, and 60 (40%) were case reports. The number of reports that provided information for neonates, infants, children, and adolescents was 9, 38, 120, and 52, respectively. Therefore, although neonates and infants are expected to have the most considerable differences in DDI potential relative to adults, limited DDI data exist for these pediatric age groups.[12]

Potential Differences in DDI Magnitude Between Pediatric Patients Relative to Adults

The magnitude of a DDI in pediatric patients may differ from adults due to age-dependent physiological processes that potentially impact a drug's PK and PD. Depending upon the physiological processes involved in the drugs' disposition and the patient population characteristics, the magnitude of DDI can widely vary between children and adults. By

comparing drug clearance (CL), area under the concentration vs. time curve (AUC), or steady-state concentrations, a published meta-analysis compared adult and pediatric DDI magnitude.[12] For 24 drug pairs (data from 31 pediatric and 33 adult DDI studies), the authors reported that the DDI magnitude was higher, similar, or lower for 10, 15, and 8 of the cases, respectively.[12] Therefore, based on potential differences in DDI magnitude relative to adults, DDI evaluation in pediatric patients requires careful consideration of drug, patient population, and methodological considerations, which we have discussed below and summarized in Figure 1.

Drug-Related Considerations

Concomitant use of drugs can result in either PK- or PD-mediated DDIs. In either case, it is essential to understand how drug-related properties affect the PK/PD and DDI magnitude in pediatric patients. Elucidating the relationship between a drug's properties and expected age-dependent differences in PK/PD could inform potential extrapolation of the magnitude of a DDI from adults to children. Such considerations should be made judiciously depending upon the type of DDI and the drugs' intended use. A previously published review article by Salem et al. performed a comprehensive literature search through 2011, and summarized pediatric DDIs reported in the literature.[12]

PK-Mediated DDIs—The mechanism of DDIs often involves a perpetrator drug that affects the PK of a victim drug by altering its absorption, distribution, metabolism, or excretion (ADME) *in vivo*. Elimination-mediated DDIs (eDDI) have received significant attention in drug development as these DDIs can directly influence CL.[13–16] Although eDDIs have been characterized to the greatest extent among all DDIs that alter ADME processes, limited data are available for eDDIs in children. Therefore, eDDI assessment in children often relies on adult data[12], and the objective is to understand whether the magnitude of the DDI observed in adults is similar and clinically relevant in pediatric patients.

The clinical relevance of an eDDI would primarily depend on two factors: (1) the extent of the eDDI (i.e., the fold-change in CL) and the (2) therapeutic window of the drug for a given indication. The narrower the therapeutic window, the more likely a fold-change in CL will warrant a dose adjustment. For instance, phenytoin (a first-generation anti-epileptic drug) is much more susceptible to eDDIs than oxcarbazepine (a second-generation anti-epileptic drug) because of its narrow therapeutic window.[17,18] Altered phenytoin exposure can result in neurological adverse events or recurrent seizures (i.e., treatment failure). The therapeutic window is related to a drug's PD properties, which might vary in children due to maturation and/or sensitivity of the pharmacological target(s). Therefore, information about the victim drug's therapeutic window in pediatric patients can help assess the clinical relevance of a DDI. Often the therapeutic window is assumed to be similar to adults in the absence of data to refute this assumption. In this scenario, the eDDI magnitude in children dictates the clinical relevance of a DDI.

In the absence of clinical data, quantitative approaches are helpful to predict the eDDI magnitude in the target pediatric population. In the case of reversible metabolic inhibition,

the eDDI magnitude as determined by a fold increase in CL (R_{CL}) is driven by two factors: fraction of dose of the victim drug eliminated by the perpetrated enzyme ($f_{e,dose}$), and the *in vivo* concentration of the perpetrator drug (I), as approximated by a "static" model in Equation 1.[19–21] The model ignores the time-dependent variation in the perpetrator drug's concentration, thereby assuming it "static" at the site of elimination. A "static" concentration (I) is analogous to the concept of an "average" steady-state concentration (while the actual steady-state concentration fluctuates with time), which is the measure of exposure often used for DDI evaluations. When an equivalent exposure (I) of the perpetrator drug is targeted in children assuming a similar exposure-response relationship between children and adults, R_{CL} will differ in children if $f_{e,dose}$ differs relative to adults. Even in the case of non-equivalent exposure (I) in children, at least for the "strong" inhibitors, R_{CL} is rate-limited by $f_{e,dose}$, since in this case, Equation 1 is approximated by Equation 2 due to a high $\frac{I}{K_i}$ ratio. Here, K_i represents the reversible inhibition constant.

$$R_{CL} = \frac{1}{\frac{f_{e,dose}}{\left[1+\frac{I}{K_i}\right]} + (1 - f_{e,dose})} \quad (1)$$

When $I >> K_i$ (for strong inhibitors),

$$R_{CL} = \frac{1}{(1 - f_{e,dose})} \quad (2)$$

Since, $\left[1+\frac{I}{K_i}\right] \approx \infty$

Under such circumstances, extrapolation of an eDDI would be simplified to extrapolation of $f_{e,dose}$ from adults to children. Therefore, to evaluate a pediatric eDDI by leveraging adult data, it is of utmost importance to understand age-related variation in $f_{e,dose}$.

Theoretically, $f_{e,dose}$ can vary early in life due to multiple factors, including the ontogeny of metabolic pathways and renal function maturation. Ontogenic maturation of different drug-metabolizing enzymes does not occur at the same rate. For instance, the fractional expression (relative to adults) of CYP2C9 is 0.17 at birth, whereas it is negligible for CYP1A2; however, the latter matures faster than the former.[22] Because of the differential maturation, the $f_{e,dose}$ of the respective enzymes (for a shared substrate) would drastically change from birth to adulthood. As quantified by Salem et al.[22], if the drug-metabolizing enzymes CYP2C9 and CYP1A2 exclusively metabolize a hypothetical drug A, with the majority of the dose being eliminated by CYP1A2 in adults ($f_{e,dose} > 0.90$), then the contribution of these two enzymes will be almost equal at birth (i.e., $f_{e,dose}$ would be approximately 0.50 for both isoforms). These authors further estimated that inhibition of the CYP2C9 pathway would have a limited impact on the AUC of drug A (~5% increase) in adults, whereas, in neonates, it would cause a 2.1-fold increase in the AUC due to a higher

$f_{e,\,dose}$ for CYP2C9 in neonates. On the contrary, for a different hypothetical drug B that is equally metabolized by CYP3A4 and CYP2D6 at birth (i.e., $f_{e,\,dose} = 0.50$), the AUC ratio would increase from 1.9-fold at birth to 4.7-fold in adults, if the CYP3A4 pathway is inhibited by a perpetrator. This suggests that the clinical relevance (or irrelevance) of an eDDI in children depends on the victim drug's metabolic pathways and the child's age. Drugs that are metabolized by CYP3A4 may also be substrates for CYP3A7 in neonates and young infants. The switch from CYP3A7 to CYP3A4 has been reported to occur in the first 3 months of life, which can impact CL predictions.[23]

If renal excretion also plays a role in the overall elimination of drug A in the above example, the $f_{e,\,dose}$ for the CYP2C9 pathway may further increase in neonates and infants (relative to adults) due to immature renal function. Therefore, careful consideration is required when extrapolating an eDDI for a partially renally cleared drug because the eDDI magnitude can be higher in neonates and infants relative to what is expected based on sole consideration of drug-metabolizing enzyme ontogeny. One study applied a sigmoidal hyperbolic model to characterize the relationship between post-menstrual age and glomerular filtration rate.[24] The authors reported that the time to half the adult value of glomerular filtration rate occurred at 47.7 weeks of post-menstrual age, suggesting that maturation in renal function will be an important predictor of clearance in neonates and infants.[24] Another study developed an ontogeny function based on postnatal age, gestational age at birth, and body weight, and identified birth as an important determinant of glomerular filtration rate for pediatric patients less than 105 weeks post-menstrual age.[25] Another important consideration is that body size-related developmental changes in organ size, composition, and perfusion occur disproportionately with age. As a result, the effect of age on the three variables that alter hepatic CL (i.e., hepatic intrinsic clearance $[CL_{int,\,H}]$, free fraction in blood $[f_{u,\,b}]$, and hepatic blood flow $[Q_H]$) are not proportional to each other, which could affect the extraction ratio (E_H) of the victim drug in different age groups. Using the Simcyp Simulator, one analysis demonstrated that such age-dependent physiological changes decrease the E_H of midazolam from 0.6 in adults to 0.02 at birth.[26] Therefore, in the case of midazolam, it would be classified as an intermediate extraction drug in adults and a low extraction in neonates. Furthermore, a switch from a higher extraction ratio to a lower extraction ratio may increase the risk of a DDI in neonates and infants. This occurs because as the E_H of a drug decreases, the CL becomes gradually less dependent on Q_H and more sensitive to changes in $CL_{int,\,H}$. In addition, a potential shift in the contribution of metabolic pathways early in life (e.g., a switch from CYP3A4 to CYP3A7 pathway in neonates[23]) and its probable implication on $f_{e,\,dose}$ should also be considered during DDI extrapolation. Similar mechanistic considerations need to be evaluated for other modes of eDDI in children, such as transporter-mediated DDIs.

There are fewer examples focused on characterizing absorption-related DDIs in the pediatric population, typically pertinent to poorly soluble drugs. For instance, it has been reported that concomitant administration of proton pump inhibitors (PPIs) decreases the bioavailability of posaconazole suspension (a poorly soluble systemic anti-fungal drug) by 42% in immunocompromised children, imposing a risk of invasive fungal infection.[27] It has been

hypothesized that the reduced bioavailability is due to the elevation of gastric pH by PPIs, which affects the pH-dependent solubility of posaconazole. A similar interaction with PPIs has been reported in adults for other drugs, such as atazanavir (an HIV protease inhibitor) and mycophenolate mofetil (an immunosuppressant) that often requires dosage adjustment.[28] Therefore, the effect of pH modulating agents on the bioavailability of such vulnerable drugs (with demonstrated pH-dependent solubility) warrants further investigation in the pediatric population as well. This would be particularly important because neonates, infants, and children (especially birth to 3 years of age) are reported to possess overall higher baseline gastric pH than adults based on repeated measurements taken over a 24-hour period.[29] It is not clear how this physiological variation would impact absorption-related DDIs in these pediatric age groups. There is evidence in adults that modulation of intestinal P-glycoprotein (P-gp) can alter the extent of absorption of P-gp substrates.[30–33] For example, decreased digoxin (a P-gp substrate) exposure following concomitant oral administration with rifampin (a P-gp inducer) was linked to intestinal P-gp induction.[33] In addition to absorption and elimination processes, there is evidence that transporter modulation may also alter drug distribution. For example, ketoconazole was found to increase the distribution of the protease inhibitors ritonavir and saquinavir through P-gp modulation in the blood brain barrier.[34] Since the drug transporters are subject to age-related maturation, such transporter-mediated DDIs during oral absorption may manifest to different extents in children than adults, which warrants further investigation.

PD-Mediated DDIs—PD-mediated DDIs occur at the site of action (i.e., at the receptor level), such that the perpetrator drug directly potentiates or attenuates the victim drug's effect without altering its exposure. While PK-mediated interactions are mostly considered undesired (with a few exceptions, such as ritonavir-boosted regimens of protease inhibitors[3]), PD-mediated DDIs serve as the basis of many therapeutic strategies, such as in anesthetic practice.[35] For example, general anesthetics, and opioid analgesics are often combined in routine anesthesia (i.e., synergistic); naloxone is used to reverse the effect of opioids (i.e., antagonistic); and combination regimens of antibiotics are frequently used to achieve a synergistic effect on bacterial killing.[1,2]

Since PD-mediated interactions occur at the receptor level, any possible alteration to receptor abundance in the pediatric population might have implications in exposure-response, and consequently, in DDI assessment. According to Stephenson's modified receptor occupancy theory[36–38], the significant portion of the receptor abundance is constituted by the "spare receptor" pool (or receptor reserve), which explains why the drug concentrations required for 50% receptor occupancy (K_d) and for 50% of the maximal effect (EC_{50}) are not necessarily the same. In other words, the theory explains why 100% receptor occupancy is not required for the potent agonists to elicit the maximal effect; and the higher the potency, the lower would be the EC_{50} compared to K_d. This implies that as the receptor reserve becomes more diminished, the EC_{50} will progressively increase and approach the K_d due to a rightward shift in the exposure-response curve (i.e., lowering the potency).[37] Nonetheless, if a gradual maturation of the pharmacological targets during early human life is assumed, a similar scenario of a low "receptor reserve"[36] might exist, which could

cause variation in the exposure-response profile in children depending on age. However, no previous systematic studies sought to test this hypothesis in the DDI context to the authors' knowledge.

There is some direct and indirect evidence from both preclinical and clinical studies that pharmacological targets, such as the serotonin reuptake transporter (SERT) on the presynaptic neurons and gamma-aminobutyric acid (GABA) receptors on the post-synaptic neurons, are expressed and/or function differently in children.[39,40] However, data describing the age-dependency of pharmacological targets is generally lacking.[40] Furthermore, the pharmacological targets are unknown for many central nervous system (CNS)-acting drugs. Therefore, the mechanistic underpinnings that may drive the differences in PD-mediated DDIs in children are not well understood. PD-mediated DDIs are usually assumed to be similar to adults in the absence of studies in the pediatric population. Studies are needed to characterize age-dependent changes in PD-mediated DDIs, including characterizing the ontogeny of PD targets, changes in PD endpoints in the presence of a DDI, and potential dosage adjustments that may be needed when drugs are expected to lead to a clinically significant DDI.

Patient Population Considerations

When performing a DDI evaluation in pediatric patients, patient-related factors can affect the DDI magnitude and variability. These factors include the pediatric age groups that the drug will likely be used in; the anticipated concomitantly administered drugs that could result in potential DDIs; differences in drug dosing and the resulting exposure of the perpetrator or victim drug based on factors such as age, body weight, the formulation used, or the indication; and the potential impact of genetics, obesity, life-saving interventions such as extracorporeal membrane oxygenation (ECMO), and disease-mediated changes on drug disposition and response. If the dose-exposure or exposure-response relationship(s) for the victim or perpetrator drug varies with age, this can result in potential age-dependent changes in the DDI magnitude. For an investigational drug, if these factors are considered early in the pediatric drug development program, they can inform the data analysis approach and collection of clinical data that can aid in assessing DDIs in the pediatric population.

Apart from age, the impact of pediatric formulation on the DDI magnitude should also be investigated, particularly for those poorly soluble drugs whose bioavailability is impacted by formulation, altering the dose-exposure profile. For example, the triazole anti-fungal drug posaconazole can be administered as suspension and delayed-release tablets depending on a patient's age. The suspension formulation has a lower bioavailability than the delayed-release tablets.[27] Posaconazole, a strong CYP3A inhibitor[41], can be prescribed to combat invasive fungal disease in immunocompromised patients also receiving the CYP3A substrate tacrolimus, resulting in a metabolic DDI. Although this DDI's relevance is well characterized in adults (i.e., a 3-fold dose reduction of tacrolimus is warranted)[41,42], investigation in pediatric patients is warranted. This is particularly important because a recent population PK (PopPK) study in infants and children has identified that posaconazole had a poor and saturable bioavailability when administered as the suspension formulation in children.[27] Interestingly, this study also concluded that a significant portion (>50%)

of virtual pediatric patients would fail to attain the target therapeutic exposure (trough concentration >1 mg/L for treatment of invasive fungal disease) with any feasible dose of posaconazole suspension if diarrhea is present and a gastric acid suppressant (i.e., PPI) is used concomitantly. Therefore, because of the expected lower exposure of posaconazole, the DDI's magnitude may differ in pediatric patients, potentially requiring a different dose adjustment, which needs to be investigated.

Other patient-related variables that can alter the $f_{e,\,dose}$ can also affect the magnitude of a DDI. For example, given that DDI data is generally collected from patients receiving drug treatments as part of their care, it is important to consider whether disease-mediated changes and life-saving interventions such as ECMO can play a role. Disease states can alter organ function, and in the case of ECMO, adsorption of the drug to the circuit can sequester the drug and alter its PK.[43] Additional patient variables such as obesity and genetic variation (e.g., genetic differences in genes encoding drug-metabolizing enzymes) could alter $f_{e,\,dose}$ and the DDI magnitude.

Clearance of hepatically eliminated drugs can be affected by obesity-induced nonalcoholic fatty liver disease (NAFLD). NAFLD is a range of progressive hepatic pathologies, starting with abnormal hepatocellular fatty infiltration (known as *steatosis* where liver fat is >5% of the total liver). It can progress to *steatohepatitis* (a fibro-inflammatory condition known as nonalcoholic steatohepatitis [NASH]). If not addressed, the inflammatory state can even lead to liver cirrhosis, where the loss of hepatocellular mass and function occurs. Although NAFLD's effect on drug-metabolizing enzymes has been investigated in animal studies, limited information is available for humans, where findings remain mostly inconclusive.[44] Nonetheless, based on available data, the effect of obesity on drug-metabolizing enzymes appears to be isoform-specific, with CYP3A4 decreasing and CYP2E1 increasing with obesity.[45] An isoform-specific effect of obesity on drug-metabolizing enzymes would impose a risk of altering the $f_{e,\,dose}$ of the purturbed enzyme (and hence the DDI magnitude) if that isoform is preferentially modulated (i.e., up- or down-regulated) by obesity. However, DDI evaluation in pediatric patients with obesity is currently lacking. In adults, one study found that co-administration of the CYP3A substrate, lurasidone, with the inhibitor, posaconazole, resulted in a less pronounced interaction (a lower increased geometric ratio for the total AUC) in patients with obesity as compared with normal-weight volunteers (although the inhibitory effect lasted longer).[46] While it has been established that >90% of obese adults have some degree of NAFLD[44,47], the prevalence of NAFLD in children with obesity is generally believed to be low.[48] However, a recent retrospective study (based on autopsy reports conducted between 1993 to 2003 in the county of San Diego) has estimated that NAFLD's prevalence in children and adolescents with obesity is 38%.[49] An association between NAFLD and pediatric obesity has been reported for other countries as well.[50,51] Therefore, the influence of obesity on DDI magnitude in children and adolescents with obesity is an immediate area of research with high importance, especially amidst the increasing rate of obesity in the pediatric population.[52]

There may also be differences in the concomitantly administered drugs and the victim and perpetrator drug dosing and indication across pediatric age groups. These differences

may impact the specific perpetrator drugs that should be considered when making DDI predictions and whether there are likely to be differences in victim or perpetrator drug exposure with age, leading to differences in the DDI magnitude. Therefore, patient-related variables that can affect the victim or perpetrator drug exposure or alter the $f_{e,\,dose}$ should be considered when evaluating DDI magnitude in pediatric patients.

Methodological Considerations

Non-Compartmental Analysis—In adults, DDI studies designed to evaluate a potential PK-mediated DDI often involve studying healthy volunteers using a crossover clinical trial design and an intensive PK sampling scheme. In analyzing this PK data, a non-compartmental analysis (NCA) approach is applied to compute a measure of drug exposure (i.e., AUC, maximal drug concentration) from individual concentration vs. time data. However, NCA analyses are not commonly used in pediatric DDI evaluation because of the sparse sampling scheme, especially in neonates and infants. Also, there is often variability in the number of samples and sample collection timing between subjects. Applying a "naïve-pooled approach," where all samples are assumed to come from a single patient (ignoring the inter-individual variability), is challenging to implement in pediatric DDI studies. This approach is generally not feasible because the AUC change in pediatric patients may not reflect the actual magnitude of DDI due to possible confounding effect(s) at the individual level. These confounding effects arise because of the heterogeneity in the pediatric patients studied (unlike healthy adults) and their existing standard of care therapies. Therefore, opportunities to apply traditional NCA in pediatric DDI assessment is limited.

Population Modeling—PopPK modeling can be used to characterize the disposition of a drug and account for the effect of patient covariates (e.g., body weight, age, and concomitant medications) that help to explain inter-individual variability. Using PopPK modeling, the impact of a specific covariate (e.g., interacting drug) on a PK parameter such as CL can be separated from other confounding covariates such as organ dysfunction measures. When applying PopPK modeling for DDI evaluation, selecting an appropriate parameterization for the covariate effect is of utmost importance. The choice should be made based on prior knowledge about the interacting drugs' characteristics, especially when a high inter-individual variability in the magnitude of DDI is expected in the target population. The covariate effect parameterization should also be based on study design considerations and the available covariate data (e.g., doses studied, sample size).

Modeling Concomitant Drug Use as a Categorical Covariate—In PopPK models, the effect of a DDI can be incorporated as a categorical covariate. This is accomplished by introducing a binary variable that accounts for the co-administration of the perpetrator drug.[53,54] This approach implicitly assumes that the change in CL (due to co-administration of an interacting drug) is a fixed value, which does not vary with respect to dose, age, and disease, or any other variable that potentially influences $f_{e,\,dose}$. However, this assumption may not be valid for all drugs because the dose and/or patient-related factors can also influence the magnitude of DDI depending upon the drug's disposition characteristics.

The dose of the perpetrator drug can influence the magnitude of the DDI depending on both its potency of enzyme modulation and its therapeutic dose range (that determines $[I]$). More specifically, the ratio of $[I]/K_i$ should be considered. According to Equation 1, a low and a high $[I]/K_i$ ratio would imply a weak and a strong inhibitor, respectively. Theoretically, for a weak inhibitor with a wide therapeutic dose range, the magnitude of a DDI may be dose-dependent due to incomplete inhibition at the lower doses. In contrast, less dose-dependency would be expected for a DDI that results from a strong inhibitor since complete inhibition would be achieved at a lower dose. For example, when the strong CYP3A inhibitor itraconazole is co-administered (100 mg once daily vs. 200 mg once daily for multiple days) with midazolam, midazolam's AUC increased to a similar extent (~6-fold) in both the dose groups.[55] However, in reality, the well-recognized categorization of "weak" and "strong" inhibitors may not align with low and high $[I]/K_i$ ratios given that the ratio will depend on the clinical range of concentrations and the inhibition constant. For example, the effect of itraconazole dose on midazolam AUC was more pronounced when a 50 mg single dose (~ 2-fold AUC ratio) is compared with 100 or 200 mg once daily (~6-fold AUC ratio).[55] In addition to the dose, the dosing regimen could also alter the DDI magnitude depending upon the perpetrator's half-life. The same study reported that a 400 mg single dose of itraconazole increased midazolam's AUC to a similar extent as 100 mg once daily. Therefore, when evaluating the magnitude of a DDI, one should consider the resulting exposures for varying dosing regimens.

As discussed, the magnitude of a DDI can vary due to differences in several other patient-related factors, which potentially alter the $f_{e,dose}$. For example, the $f_{e,dose}$ of a partially metabolically cleared victim drug can increase in neonates and infants due to the immature renal function. Even once the renal function is mature, organ dysfunction can also cause $f_{e,dose}$ to increase further. Apart from this, differential ontogeny rates across various enzyme isoforms (e.g., CYP3A4 vs. CYP2D6) would cause their relative expression to vary with age, resulting in variation in $f_{e,dose}$. When multiple metabolic pathways are involved (e.g., CYP3A4 vs. CYP2D6), the presence of a polymorphic allele in at least one of these contributing pathways (e.g., CYP2D6) would further increase $f_{e,dose}$ of the other pathway (i.e., CYP3A4), which contribute to variability in the DDI magnitude. In these situations, modeling the DDI using a more mechanistic framework may be warranted.

Mechanism-Based Modeling—Another strategy to model the DDI and account for the dose-effect is to co-model the perpetrator drug's PK. The perpetrator drug model is then linked to the victim drug's elimination via a fit-for-purpose enzyme modulation model.[56,57] While this approach closely aligns with the pharmacology (since the perpetrator's exposure is considered a continuous covariate in the model), its implementation is often challenging due to the lack of perpetrator concentration vs. time data, especially in children. Therefore, another approach is to capture the dose-dependent DDI effect by modeling it as an ordinal categorical covariate, accounting for each dose.[54] While the latter approach can be more readily implemented because perpetrator drug concentration vs. time data are not needed, it also reduces the power to estimate the ordinal covariate effects by sub-grouping the patients based on the dose level. Therefore, whenever data are available from multiple dose levels,

efforts should be made to account for dosing differences as a continuous covariate. Although this approach would account for dosing differences, a fundamental assumption is that there is no inter-individual variability in the average perpetrator drug exposure (equivalent [I] in Equation 1) within a dose group. Therefore, the inter-individual variability in the perpetrator drug PK is not captured. For example, a sigmoidal model where the DDI effect increases with the perpetrator drug's dose level and eventually asymptotes to a maximal effect can be applied.

In addition to the perpetrator drug dose, other continuous covariates (e.g., age, organ function) that potentially impact the DDI by causing variation in $f_{e,dose}$ between pediatric patients should also be considered. The model parameterization should be justified by the biological considerations that can contribute to drug exposure variability and take into account study design variables such as the sample size.

Early phase pediatric studies may be limited in sample size in many cases, making DDI estimation by a PopPK analysis challenging. A simulation-estimation-based exercise by Yang and Beerahee concluded that PopPK studies' power to detect the DDI would largely depend on the inter-individual variability in PK parameters.[58] Using a two-compartment model, their results indicated that for a parameter with low inter-individual variability (<25% coefficient of variation), a minimum of 40 participants would be required to achieve 90% power. The requirement will increase to at least 80 participants if the inter-individual variability on the PK parameter rises to nearly 40%. A similar trend of a higher sample size requirement for PopPK studies was reported in another simulation-estimation-based study compared to an NCA approach to achieve the required power.[59] Their overall conclusion was that typical phase 2/3 studies in drug development would allow DDI estimation by PopPK methods. Therefore, given the sample size constraints in pediatric studies, it is recommended to perform simulation-based power analysis on a case-by-case basis to design the pediatric studies for DDI assessment optimally.[54]

Physiologically-Based Pharmacokinetic (PBPK) Modeling—PBPK modeling can be applied to mechanistically account for the dose and patient-related factors that can impact DDI magnitude and variability. A PBPK model's ability to account for the mechanistic underpinnings of the biological processes that determine DDI potential, especially in the absence of clinical data in the target population, has made this modeling approach a helpful tool in drug development. The number of articles that used PBPK modeling for U.S. Food and Drug Administration (FDA) approved drugs increased by more than tenfold between 2012 and 2018.[60] Among a total of 136 FDA submissions between 2008 and 2014 that applied PBPK modeling, 61% focused on addressing DDI-related questions.[61,62] However, there are a limited number of examples of using PBPK modeling for pediatric DDI assessment. Although a few recent reports have utilized PBPK modeling to predict an eDDI in children[63–66], only one article considered a target population below two years of age.[65] As of now, the use of PBPK modeling in pediatric regulatory submissions has primarily focused on initial dose-finding for clinical trials, especially in the younger children below two years of age.[67] This could be mainly because limited pediatric DDI data are currently available to validate the PBPK model predictions, with almost no DDI data available in

neonates and infants[4], where maximum variation in the magnitude of DDI could be expected (compared to adults). Therefore, there is a clear knowledge gap in the application of PBPK modeling for pediatric DDI assessment, particularly below two years of age.

When applying PBPK modeling in the pediatric population, adult PBPK models are first developed and evaluated for the victim and perpetrator drugs. If adult DDI data are available, a joint DDI model can be implemented and evaluated.[4] These adult PBPK models are then extrapolated to the pediatric population by accounting for age-dependent physiological changes such as organ size, composition, perfusion, and function. Such age-dependent changes are already implemented in virtual pediatric populations available within software platforms such as Simcyp® and PK-Sim®. The pediatric PBPK models for the perpetrator and victim drugs can then be evaluated separately using available clinical data. However, pediatric PBPK model evaluation can be challenging due to the presence of other confounding factors that affect PK, including disease-mediated factors (e.g., organ impairment, critical illness) and/or co-medications. Accounting for these disease-mediated changes in the virtual pediatric population can be challenging due to gaps in knowledge and heterogeneity in disease status between patients. In these circumstances, it is essential to have confidence in the algorithms that define the age-dependent changes in the "rate-limiting" physiological variables to ensure an appropriate joint DDI model is developed. More specifically, in the context of DDI evaluation, essential rate-limiting variable(s) are the ontogeny of enzyme and transporter expression(s) that define the age-dependent change in $f_{e,\ dose}$ of the perturbed pathway(s) in the victim drug's model. Scientists working at the FDA have identified ontogeny as the key area where confidence needs to be built in order to make "untested" predictions of DDI in children below two years of age.[67] Additionally, the polymorphic drug-metabolizing enzymes and transporters can also be a rate-limiting variable influencing $f_{e,\ dose}$ if multiple metabolic/transport processes are involved. Extensive research has already been performed to facilitate PBPK modeling for the pediatric population. Various ontogeny equations for enzyme expressions have already been developed, and some of them are already implemented in commercial PBPK software.[68–72] Apart from drug-metabolizing enzymes, there has also been progress in elucidating the impact of ontogeny in drug transporters that can impact drug disposition.[73,74] Therefore, there is an opportunity to apply PBPK modeling to evaluate both drug-metabolizing enzyme- and transporter-mediated DDIs in the future.

Model Simulations—Developed PopPK and PBPK models can be used to evaluate the DDI magnitude in different untested scenarios using a simulation-based approach. The simulations can assess DDI magnitude differences as a function of age, dose, and genetic variation if these variables are accounted for in the PopPK or PBPK model. The simulations can inform dose adjustments based on the predicted change in the measure(s) of exposure as a function of these variables if the drug combination is used in pediatric patients. Drug exposure measures that can be simulated and related to the drug's therapeutic window include AUC and the maximal drug concentration. As described in the FDA guidance, a no-effect boundary needs to be defined, representing the interval within which a change in a systemic exposure measure is considered not relevant to warrant clinical action (e.g., dose or schedule adjustment, or additional therapeutic monitoring).[75] For clinical DDI studies,

no-effect boundaries can be derived for the substrate drug based on available information about the exposure and exposure-response relationships.[75] In the absence of information that can help define these no-effect boundaries, standard bio-equivalence criteria can be followed. As per the criteria, the 90% confidence interval for the exposure measure's geometric mean ratio (in the presence and absence of the interaction) should fall within the range of 80–125% to be considered a clinically insignificant DDI. A 90% confidence interval for the exposure measure's geometric mean ratio can be generated separately for each pediatric age group studied in pediatric DDI evaluation.

Summary of Pediatric DDI Evaluation, Knowledge Gaps, and Areas for Future Research

A DDI magnitude estimated in adults may not be directly applicable to pediatric patients under various circumstances discussed in this article. However, given that pediatric studies often employ an opportunistic study design, estimation of the DDI magnitude in pediatric age groups is challenging. Selection of an appropriate modeling approach is needed and should depend upon the availability and/or informativeness of clinical DDI data. When robust pediatric DDI data are available (i.e., adequate sample size and sampling scheme), a top-down analysis that uses population modeling can be applied since it has the unique ability to estimate the PK and PD parameters from opportunistic datasets. Population modeling can also help to discern the effect of concomitant medication(s) on the inter-individual variability in drug disposition or response. The use of population modeling for pediatric DDI evaluation is mainly limited by small sample sizes and scarcity of information about co-medications (i.e., dose levels, perpetrator drug PK data). On the other hand, PBPK modeling holds great promise for pediatric DDI evaluation, particularly when clinical DDI data are unavailable (or are less informative). PBPK modeling can be applied to make PK predictions by integrating available drug and physiological data of the target population and accounting for study design variables. As summarized in Figure 2, population and PBPK modeling approaches each have strengths and limitations, and both will play a role in pediatric DDI evaluation.

Collaborative research is needed to facilitate pediatric DDI evaluation in the future. This can include characterizing patient-related variables' (e.g., obesity, organ dysfunction, genetic variation) impact on DDI magnitude; the development and refinement of virtual pediatric patient population libraries; continued research into the maturation of enzyme and transporter proteins; and pediatric DDI data collection for model development and evaluation. PBPK modeling predictions require virtual patient population libraries of physiological variables for the target population that account for the inter-individual variability in PK. These virtual patient population libraries should account for physiological changes that mimic different real-world patient populations, such as pediatric patients with obesity, organ dysfunction, and critical illness. When comparing PBPK model predictions with real-world patient data, model evaluation can be challenging if these patient-related variables are not captured. Therefore, continued development and refinement of virtual patient population libraries is needed for PBPK model evaluation purposes.

Additional potential areas for research include identifying elimination pathways and/or combination of elimination pathways that may be particularly susceptible to DDIs in

pediatric patients; identifying ideal clinical substrates, inhibitors, and inducers (that are routinely administered per standard of care in pediatric patients) to validate DDIs associated with these elimination pathways; and more examples demonstrating the use of opportunistic and electronic health cord data for pediatric DDI evaluation. Also, much more research is needed to characterize PD-mediated DDIs in pediatric patients, including applying methodologies that have been used to assess PD-mediated DDIs in adults.[35,76–79] Finally, the potential ontogeny of pharmacological targets and its impact on PD-mediated DDIs has remained unexplored to the authors' knowledge. Initiatives to facilitate collaboration between drug developers, academic researchers, and regulatory agencies can help expedite the research in these unmet areas of pediatric DDI evaluation.

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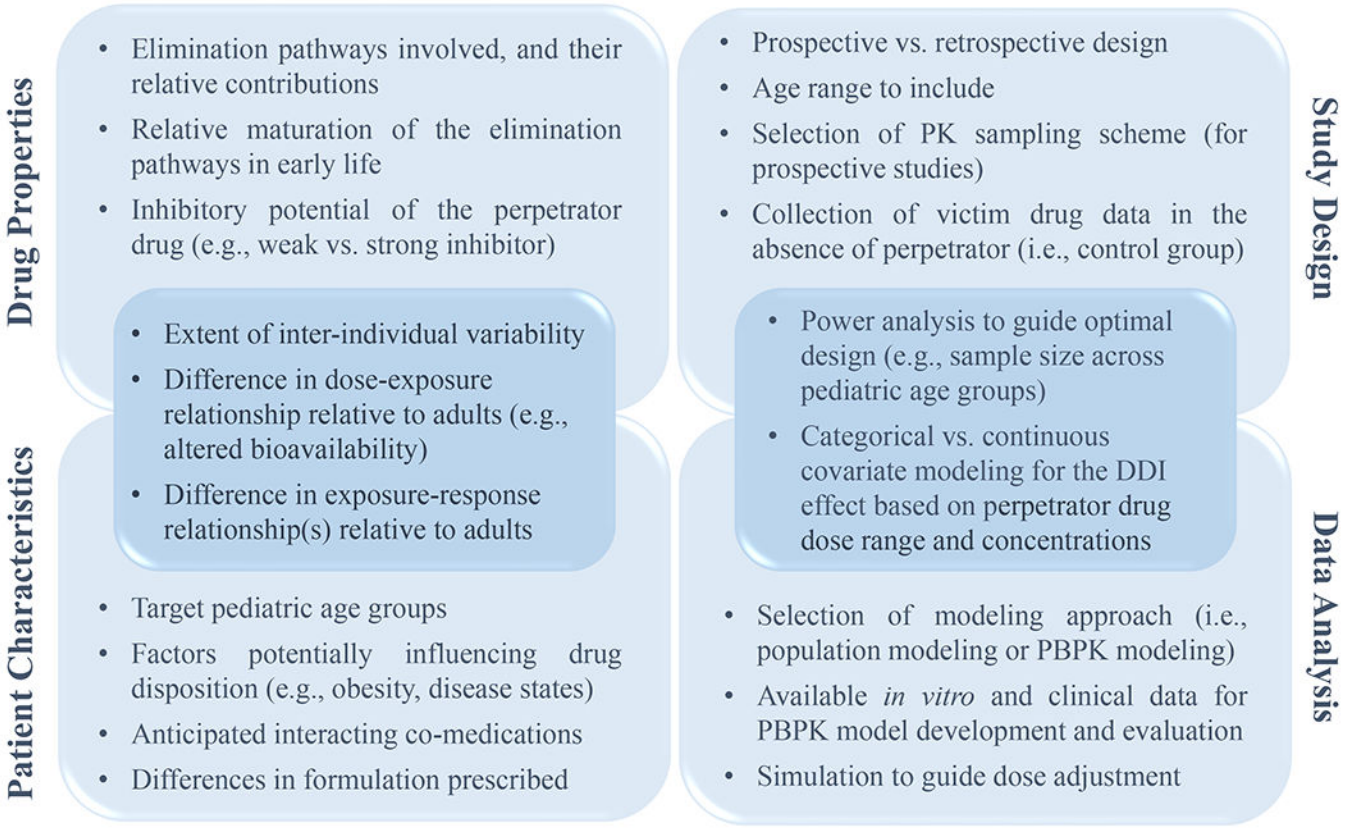

Figure 1.

Essential considerations for the evaluation of pediatric drug-drug interactions (DDIs). The drug, patient population, study design, and data analysis considerations are summarized within separate light blue boxes. The study design and data analysis categories collectively represent the methodological considerations. The considerations outlined within the dark blue boxes are common to the corresponding categories in the light blue boxes. PK, pharmacokinetic; PBPK, physiologically based pharmacokinetic.

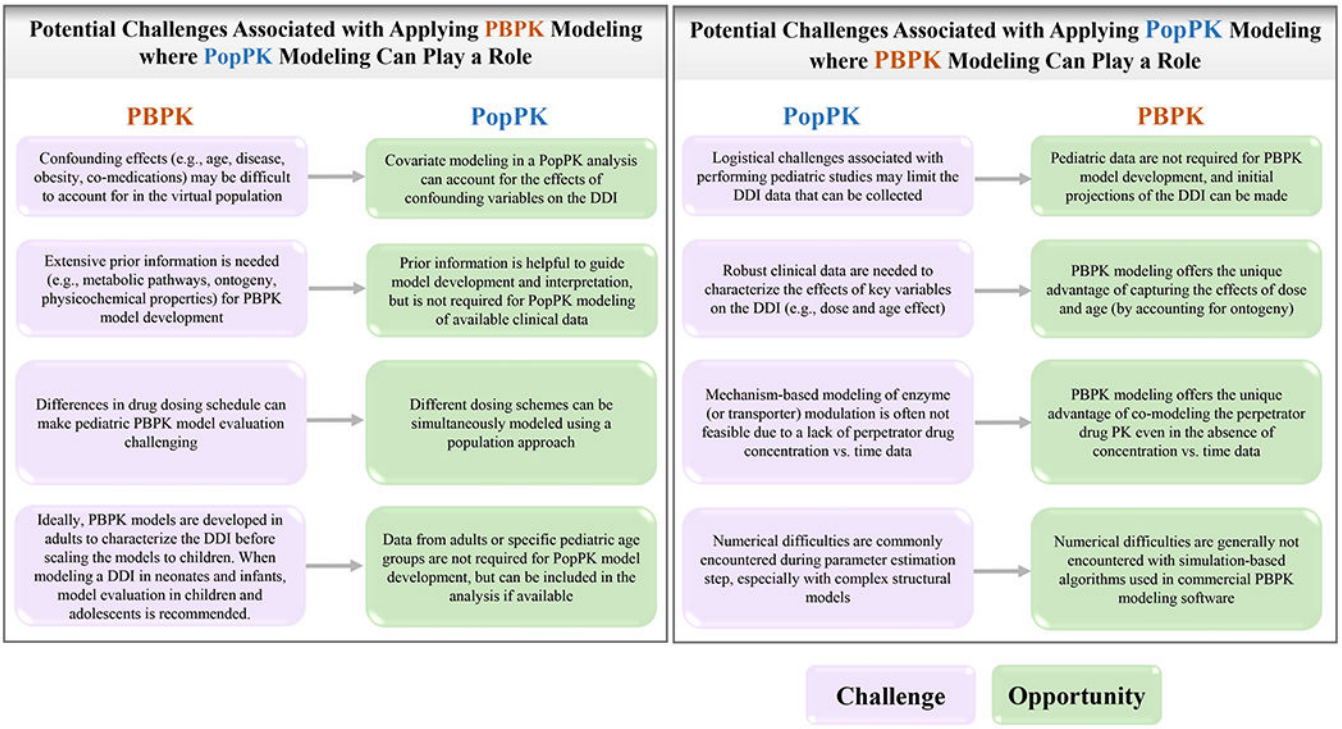

Figure 2.

Challenges and opportunities for applying physiologically based pharmacokinetic (PBPK) and population pharmacokinetic (PopPK) modeling in pediatric drug-drug interaction (DDI) evaluations.

Table 1.

Comparison of the key attributes between adult and pediatric drug-drug interaction (DDI) evaluation and their implications in pediatric DDI assessment.

	Adults	Pediatric Patients	Implications for Pediatric DDI Assessment
Study subjects	Healthy volunteers	Patients receiving the drugs as part of their treatment regimen	Potential confounding effects of disease states and co-medications may be observed.
Study design	Prospective (crossover or parallel, two-arm study design)	Prospective, retrospective, or case reports	Findings may be limited by the study design variables in retrospective studies (e.g., limited dose and age range, the limited sample size for each age or dose group).
Physiological changes with age	Generally, not a significant factor for healthy volunteers	Present throughout childhood	Age-dependent physiological changes may confound the DDI magnitude if the age effect is not captured (most relevant for <2 years of age due to possible alteration of $f_{e,dose}$).
PK data analysis approach	Non-compartmental analysis, Population PK, or PBPK	Population or PBPK modeling	Study design variables (e.g., sample size, perpetrator's PK data, or dose range) should guide population modeling methodology (e.g., categorical vs. continuous covariate modeling). PBPK modeling is an alternative approach when clinical DDI data are unavailable or less informative.
PK sampling	Intensive	Sparse	Sparse sampling makes it challenging to apply a non-compartmental analysis approach.

PK: pharmacokinetic; PBPK: physiologically-based pharmacokinetic; $f_{e,dose}$: fraction of dose of the victim drug eliminated by the perpetrated elimination pathway.