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REVIEW

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# Clinical pharmacokinetics of antipsychotics in pediatric populations: a scoping review focusing on dosing regimen

Jiayi Liang[a,b,c*], Lisa T. Ringeling [a,b,d*], Rebecca A. Hermans[a,b,d], Izgi Bayraktar[b], Tessa M. Bosch[a,c,e], Karin M. Egberts[f], Sanne M. Kloosterboer [d], Brenda de Winter[a,b], Bram Dierckx[d] and Birgit C.P. Koch[a,b]

[a]Rotterdam Clinical Pharmacometrics Group, Erasmus University Medical Center, Rotterdam, the Netherlands; [b]Department of Hospital Pharmacy, Erasmus University Medical Center, Rotterdam, the Netherlands; [c]Department of Hospital Pharmacy, Maasstad Hospital, Rotterdam, the Netherlands; [d]Department of Child and Adolescent Psychiatry/Psychology, Erasmus University Medical Center, Rotterdam, the Netherlands; [e]Department of Clinical Pharmacology & Toxicology, Maasstad Lab, Maasstad Hospital, Rotterdam, the Netherlands; [f]Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, Center of Mental Health, University Hospital Würzburg, Würzburg, Germany

**ABSTRACT**

**Introduction:** Achieving optimal clinical responses and minimizing side effects through precision dosing of antipsychotics in children and adolescents with psychiatric disorders remains a challenge. Identifying patient characteristics (covariates) that affect pharmacokinetics can inform more effective dosing strategies and ultimately improve patient outcomes. This review aims to provide greater insight into the impact of covariates on the clinical pharmacokinetics of antipsychotics in pediatric populations.
**Areas covered:** A comprehensive literature search was conducted, and the main findings regarding the effects of the covariates on the pharmacokinetics of antipsychotics in children and adolescents are presented.
**Expert opinion:** Our study highlights significant covariates, including age, sex, weight, CYP2D6 phenotype, co-medication, and smoking habits, which affect the pharmacokinetics of antipsychotics. However, the findings were generally limited by the small sample sizes of naturalistic, open-label, observational studies, and the homogeneous subgroups. Dosing based on weight and preemptive genotyping could prove beneficial for optimizing the dosing regimen in pediatric populations. Future research is needed to refine dosing recommendations and establish therapeutic reference ranges critical for precision dosing and Therapeutic Drug Monitoring (TDM). The integration of individual patient characteristics with TDM can further optimize the efficacy and safety of antipsychotics for each patient.

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**KEYWORDS**
Antipsychotics; pharmacokinetics; child; adolescent; pediatrics; covariates

## 1. Introduction

Antipsychotic drugs have been proven effective for the treatment of a wide range of psychiatric disorders in children and adolescents. Various studies have shown rising trends of antipsychotic use among the pediatric population [1–3]. However, the high incidence of adverse effects and suboptimal treatment outcomes exert substantial limitations on the prescription of antipsychotic drugs. The growing attention toward pharmacokinetic research in pediatric populations [4] and the relationship between pharmacokinetics, drug exposure and clinical outcome has prompted our interest in identifying the predictive value of patient characteristics (covariates) in the optimization of dosing strategies of antipsychotics to attain better clinical responses and to minimize preventable side effects.

There are significant physiological differences between children and adults, which can lead to age-related differences in pharmacokinetics and pharmacodynamics. Children have a smaller volume of distribution, immature organ systems and drug-metabolizing enzymes, and accelerated elimination compared to adults [5–9]. These differences can become even more pronounced during puberty as hormonal changes affect drug clearance and drug serum concentrations. As the majority of clinical studies are conducted in adults, pediatric dosages are often unknown and extrapolated from adult data [5]. According to the review of Fekete et al. [10] of the available pharmacokinetic literature on psychoactive drugs, there are considerable differences in the plasma concentrations for a given dose between children or adolescents and adults. Moreover, studies have shown that treatment with antipsychotic drugs during developmental hormonal and neurobiological changes in patients may result in adverse drug reactions (ADRs) that are not observed in adults at the same frequency or at all [11]. Overall, this will impair the drug's efficacy and safety in the younger population.

In light of these findings, better-informed dosing strategies for antipsychotic drugs in the pediatric population are necessary. In this scoping review, we aim to provide an overview of

**CONTACT** Jiayi Liang j.liang@erasmusmc.nl; Lisa T, Ringeling l.ringeling@erasmusmc.nl Erasmus MC, University Medical Center Rotterdam, Wytemaweg 80, PO box 2060, Rotterdam 3000, The Netherlands
*These authors contributed equally.

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**Article highlights**

- Limited research on the safety, efficacy, and pharmacokinetics of antipsychotic drug dosing regimens in pediatric populations makes it difficult for clinicians to determine the optimal dosing regimen.
- Most antipsychotic drugs show a linear relationship between drug dose and plasma drug concentrations.
- Key findings suggest that CYP2D6 metabolism affects the pharmacokinetics of risperidone, while concomitant medications influence the pharmacokinetics of olanzapine. CYP3A4-interacting drugs primarily influence quetiapine plasma concentration. Smoking habits and female sex affect clozapine exposure, and aripiprazole exposure is negatively correlated with CYP2D6 metabolism.
- The influence of covariates on pharmacokinetics is heterogeneous and has been poorly reported for most antipsychotic drugs.
- Novel techniques, such as model-informed precision dosing, integrated with individual patient characteristics could aid in adjusting doses in pediatric populations using antipsychotics.

potential significant covariates, such as age, sex, pharmacogenomics, and body weight, in relation to the clinical pharmacokinetics of antipsychotics in this population. The potential impact of different covariates on the pharmacokinetics and ultimately, the dosing regimen of antipsychotics is discussed, and an expert opinion is given. Along with what is known about specific therapeutic reference ranges, this review aims to provide clinicians and pharmacists guidance in the dosing of antipsychotics in this vulnerable population.

## 2. Methods

### 2.1. Information sources

A literature search was performed in May 2022, and updated in March 2023 by the Erasmus MC Medical Library to obtain all the available literature on the clinical pharmacokinetics of antipsychotics in children and adolescents. Six databases (Embase, Medline All Ovid, PsycINFO, Web of Science Core Collection, Cochrane Central Register of Controlled Trials, and Google Scholar) were searched. Detailed search terms can be found in supplementary file 1.

### 2.2. Eligibility criteria and study selection

Studies reporting the effects of covariates (i.e., age, sex, weight/BMI, enzyme-inhibiting/inducing co-medication, CYP2D6 polymorphism, and smoking habits) on antipsychotic drug concentration in children and adolescents aged up to 18 years old were eligible for inclusion. The eligibility criteria are presented in Table 1. The title and abstract were independently screened by two reviewers to select relevant publications; any discrepancies were resolved through a consensus discussion. In addition, the references of identified articles were checked for relevant studies.

### 2.3. Data collection process

The following data were retrieved from the included studies: author, year of publication, number of subjects, characteristics of study participants (sex, age, and diagnosis), study design, studied drug, outcome measures, covariates, and the study results.

## 3. Results

### 3.1. Study selection

Figure 1 shows a flowchart of the selection process. The literature search resulted in 3366 articles after removing duplicates. The exclusion process was performed according to the article of Bramer et al. [12]. Title and abstract screening resulted in 46 articles describing the pharmacokinetics of antipsychotics in the pediatric population. Backward citation screening yielded two additional publications, providing 48 publications in total. These included articles discuss 12 antipsychotics: risperidone, olanzapine, quetiapine, clozapine, aripiprazole, asenapine, chlorpromazine, haloperidol, lurasidone, pipamperone, tiapride, and ziprasidone. The included articles are listed in supplementary file 2, Table S1. The influences of different covariates on the drug concentrations of the respective antipsychotics are included in the overview (Table 2).

### 3.2. Covariates as predictors of the pharmacokinetics of antipsychotics drugs

#### 3.2.1. Main findings per antipsychotic drug

Among the available literature on the pharmacokinetics of antipsychotics in children and adolescents, risperidone and olanzapine were the most widely studied drugs, followed by quetiapine, clozapine, and aripiprazole. The main findings for the respective antipsychotics are described below. Regarding the remaining antipsychotics (asenapine, chlorpromazine, haloperidol, lurasidone, tiapride, pipamperone, and ziprasidone), due to limited available literature, findings on the potential correlations of covariates and drug concentrations were inconclusive.

Table 1. In- and exclusion criteria for study selection.

| Inclusion criteria | Exclusion criteria |
|---|---|
| The study concerns antipsychotics | No analysis on relation between drug concentrations and relevant covariates |
| The study is performed in children and adolescents | Drug is used for non-psychiatric indications |
| Drug plasma or serum levels are measured and reported | Non-human subject |
| Clinical pharmacokinetics are reported | Maternal use during pregnancy and lactation |
| Only original research output | Studies focusing on toxicology/overdoses |
| Full-text available | Case reports |
| | Conference papers and abstracts |
| | Post mortem studies |

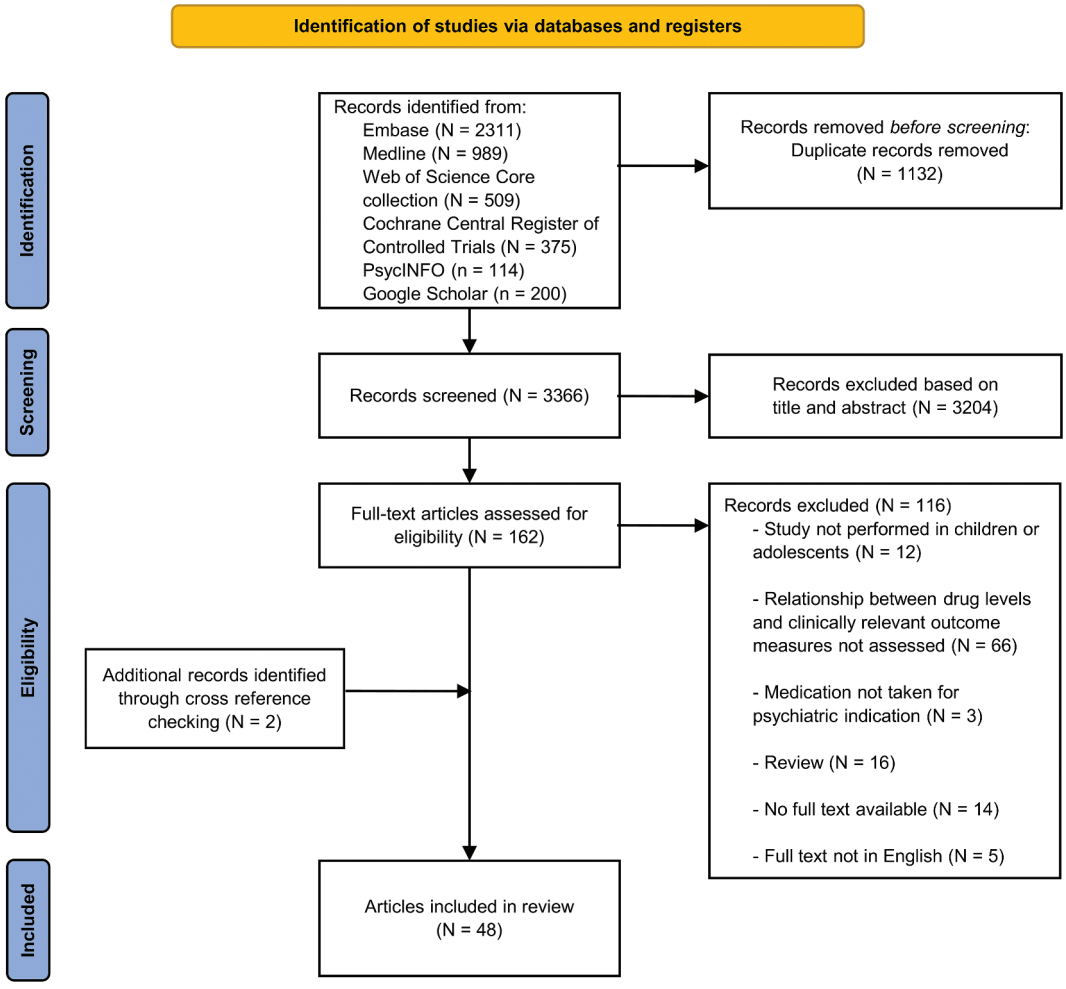


Figure 1. Flowchart of the selection process.

### 3.2.2. Risperidone

The majority of the studies have demonstrated linear pharmacokinetics for risperidone and its active metabolite 9-OH-risperidone (9-OH-RIS) [16,44–48]. Furthermore, the influence of age, sex, weight, co-medication, and CYP2D6 polymorphism on the pharmacokinetics of risperidone has been extensively studied.

Firstly, studies showed different results on the influence of age on the pharmacokinetics of risperidone and 9-OH-RIS. While the majority of the studies reported lower plasma concentrations or concentration-dosage (C/D) ratios in children compared to adolescents or adults [16,44,46,47], one study reported the opposite effect [51]. However, it is important to note that these studies did not take into account the normalization for body weight to minimize the potential effects of developmental changes in body mass and composition. Among the five studies that did not identify a significant correlation between age and risperidone exposure, the majority used dose-corrected serum concentration normalized to body weight [33,45,55,57,58].

Regarding the influence of sex, two studies measured higher concentrations of the active moiety ($RIS_{am}$, the sum of risperidone and 9-OH-RIS) in females, despite receiving similar dosages of risperidone to males [33,47]. However, the majority of the studies found no significant differences [45,48,49,57,58] or even a positive correlation between the male sex and the serum concentration of risperidone [44]. Remarkably, the study populations were predominantly male [44,45,48,49,57].

As for body weight and BMI, the majority of the studies found no significant correlation between weight and the serum concentrations of risperidone, 9-OH-RIS, or $RIS_{am}$ [45,47,48,58]. Two studies reported a positive association between weight and concentrations of 9-OH-RIS and $RIS_{am}$ [44,49]. In contrast, Sherwin et al. [51] observed a positive association between the clearance of 9-OH-RIS and body weight, suggesting lower plasma concentrations with increasing weight.

Several studies found an effect of concomitant medication use on risperidone concentrations [33,44,50]. Among different drugs affecting the CYP450 enzyme system studied by Aichhorn et al. [33] (i.e. biperiden, valproate, sertraline, fluoxetine, paroxetine, citalopram, and venlafaxine), only valproate had a significant effect on the risperidone serum concentration. Concomitant use of valproate resulted in a 55% higher C/D ratio of risperidone compared to those

Table 2. Literature overview ($n = 48$) of the findings on the correlation between covariates and the serum concentrations of respective antipsychotic drugs.

| Antipsychotic drug | Covariates | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Daily dose (linear pharmacokinetics) | Age | Sex | Weight/ BMI | (Enzyme-inhibiting/ Inducing, number of) co-medication | Higher CYP2D6 metabolic capacity | Smoking habits | Treatment duration |
| **Aripiprazole (n = 7)** | Bachmann[13] Egberts[14] Findling#[15] Pozzi[16] Ma[17] | Egberts[14] | Egberts (♀)[14] | Xin[18] | Pozzi[16] | Rudå [19] Xin[18] | Bachmann[13] Egberts[14] | |
| | | Bachmann[13] Findling[15] Pozzi[16] | Bachmann[13] Ma%[17] | Bachmann[13] Egberts[14] | Bachmann[13] Egberts[14] Rudå[19] | | | |
| **Asenapine (n = 1)** | | Dogterom[20] | Dogterom[20] | Dogterom[20] | | | | |
| **Chlorpromazine (n = 1)** | | Rivera#[21] | | | Rivera#[21] | | | |
| **Clozapine (n = 5)** | Couchmann[22] Frazier#[23] Sporn[24] Wohkittel[25] | Wohkittel[25] | Couchmann(♀)%[22] Frazier (♀)#%[23] Wohkittel (♀)[25] | Couchmann[22] | Wohkittel[25] | | Couchmann [22] Wohkittel[25] | |
| | | Couchmann[22] Frazier#[23] | Alfaro#[26] | | | | | |
| **Haloperidol (n = 2)** | | Morselli#[27] | Alfaro#[26] | | | | | |
| **Lurasidone (n = 1)** | Findling[28] | Findling[28] | | | | | | |
| **Olanzapine (n = 9)** | Fekete[29] Grothe[30] Patel[31] Theisen[32] | Aichhorn [33] Maharaj[34] Patel[31] | Lobo (♀)[35] Xiao (♀)[36] | Lobo[35] | Theisen[32] Xiao[36] | | Aichhorn [33] Theisen[32] | |
| | | Fekete[29] Grothe[30] Lobo[35] Theisen[32] Xiao[36] | Aichhorn#% [33] Alfaro[26] Fekete[29] Maharaj [34] Theisen [32] | Maharaj[34] Fekete[29] Xiao[36] | Aichhorn[33] Fekete[29] | | Fekete[29] Lobo[35] Xiao[36] | |
| **Pipamperone (n = 1)** | Kloosterboer[37] | | | Kloosterboer[37] | | | | |
| **Quetiapine (n = 7)** | Albantakis[38] Gerlach#[39] Winter[40] Yang[41] | Castberg[42] | Albantakis[38] Castberg#[42] Gerlach#[39] Yang%[41] | Yang[41] | Castberg*[42] | Rudå[19] | Albantakis[38] | |
| | Findling#[43] | Albantakis[38] Findling#[43] Winter[40] Yang[41] | | Albantakis[38] | Castberg*[42] Albantakis [38] Rudå[19] Yang[41] | | | |
| **Risperidone (n = 19)** | Calarge[44] Klampfl[45] Medhasi[46] Piacentino[47] Pozzi[16] Taurines[48] | Calarge[44] Medhasi[46] Piacentino[47] Pozzi[16] | Aichhorn(♀)[33] Calarge (♂)%[44] Piacentino (♀)[47] | Calarge[44] Kloosterboer[49] | Aichhorn[33] Calarge[44] Dos Santos[50] | Medhasi[46] Sherwin[51] Troost[52] Vanwong[53] Vanwong,[54] | Taurines[48] | Kloosterboer[49] |
| | | Sherwin[51] | | Sherwin[51] | | | | |
| | Gagliano#[55] Kent[56] | Aichhorn[33] Fekete[57] Gagliano[55] Klampfl[45] Thyssen[58] | Fekete%[57] Klampfl%[45] Kloosterboer% [49] Taurines%[48] Thyssen[58] | Klampfl[45] Piacentino[47] Taurines [48] Thyssen[58] | Kloosterboer[49] Taurines[48] | | Klampfl[45] Kloosterboer[49] | Calarge[44] Medhasi[46] |
| **Tiapride (n = 1)** | Fekete [59] | Fekete[59] | Fekete%[59] | Fekete[59] | Fekete[59] | | | |
| **Ziprasidone (n = 1)** | Sallee#[60] | Sallee#[60] | Sallee#%[60] | | | | | |

Positive correlation with serum concentration ( ↑ )
Negative correlation with serum concentration ( ↓ )
No (significant) correlation with serum concentration ( - )
(n=), number of articles; #, sample size n < 30; ♀, female; ♂, male; *, the PK effect is concomitant drug-dependent; %, unequal distribution of sex.

in non-valproate users. In another study, concomitant use of CYP2D6-inhibiting drugs resulted in significantly higher risperidone concentrations and lower 9-OH-RIS concentrations, whereas there was no difference in $RIS_{am}$ [48]. Calarge and Miller [44] and Dos Santos et al. [50] also found a significant impact of CYP2D6-inhibitors on risperidone exposure, however, to a lesser extent on its metabolite. The study results regarding the role of CYP2D6 phenotypes on the pharmacokinetics of risperidone were consistent. Higher CYP2D6 metabolic capacity resulted in significantly lower risperidone plasma concentrations and RIS/9-OH-RIS ratio [51–54]. Although not significant, Vanwong et al. [54] found a corresponding trend of a higher 9-OH-RIS plasma concentration with higher CYP2D6 metabolic capacity. In addition, Medhasi et al. [46] found a strong relationship between CYP2D6 variants (c.1846 G > A rs3892097, C. 100C > T rs1065852, c. 2988 G > A rs28371725) and the metabolism of risperidone.

### 3.2.3. Olanzapine

For olanzapine, a positive correlation between daily dose and serum concentration was found, indicating linear pharmacokinetics [29–32]. Remarkably, the studied effects of age, sex, weight, enzyme inhibiting/co-medication, and smoking habit, showed contradictory findings.

Regarding age, the majority of the studies showed no differences in the serum concentration and pharmacokinetics of olanzapine between adolescents and adults [29,30,32,35,36]. However, several other studies found a negative correlation between age and serum concentrations

of olanzapine [31,33,34]. Aichhorn et al. [33] found a significantly higher (~40%) weight-corrected C/D ratio in adolescents compared to adults. In a prospective population pharmacokinetic (popPK) model study, the postmenstrual age was found to be an influential covariate for clearance, but postnatal age showed no effect [34]. A major limitation of this study was that other potentially influential covariates (i.e. weight, interacting medications and smoking habit) were left out.

Concerning sex, one study found a higher clearance in male pediatric patients compared to females, resulting in higher dosages (>15 mg per day) for males to reach the therapeutic window [36]. This result is supported by the finding of Lobo of a 30% higher clearance in men compared to females [35]. In contrast, several other studies found no significant differences between the sexes [26,29,32–34]. However, given the small sample size of some studies and the study populations being predominantly male, the validity of this conclusion is questionable.

In a popPK model study, body weight was found to be an influential covariate for the developmental changes in clearance, showing a positive correlation between body weight and clearance, resulting in lower serum levels of olanzapine [34]. Another popPK study found a statistically significant effect of weight on pharmacokinetics in adolescents, showing a substantial degree of interpatient variability in clearance, with a negative correlation between body weight and serum levels of olanzapine [35]. Two other studies did not identify weight as a significant covariate on serum concentration [29,36].

In the study of Theisen et al. [32], the concomitant use of serotonin reuptake inhibitors (SSRIs) resulted in a 38% higher C/D ratio compared to monotherapy, whereas Xiao et al. [36] observed a significant decrease in the serum olanzapine concentration with concomitant use of valproate. Two studies found no significant effect of co-medications such as antipsychotics, antidepressants, and benzodiazepines on C/D ratios of olanzapine [29,33]. The effect of smoking habits on olanzapine exposure remains ambiguous. In two studies, smokers exhibited a lower C/D ratio compared to nonsmokers [32,33], whereas in other studies, statistical significance was not attained [29,35,36]. Some of these studies are limited due to a relatively small number of smokers to draw conclusions on significance.

#### 3.2.4. Quetiapine

Predominantly, a dose-dependent increase in serum concentration was observed, indicating linear pharmacokinetics [38–41]. However, the study of Findling et al. [43], despite having a small sample size, did not observe any statistically significant relationships between pharmacokinetics and dosage. The majority of the results concerning age did not demonstrate any association with quetiapine exposure [38,40,41,43]. However, Castberg et al. [42] observed a 31% lower C/D ratio in the younger age group compared to the age group of 18–69 years, although it was not corrected for weight. Several studies have found that the covariate sex does not affect the plasma concentration of quetiapine [38,39,41,42]. The most notable results are related to concomitant medication. Castberg et al. [42] found an association between an increased C/D ratio of quetiapine and use of (es)citalopram (↑16%), alimemazine (↑28%), clozapine (↑82%), and fluvoxamine (↑159%), whereas a decreased quetiapine C/D ratio was associated with carbamazepine (↓86%), lamotrigine (↓17%), levomepromazine (↓20%), and oxazepam (↓21%). The variation in C/D ratios with different co-medications could be attributed to CYP3A4–drug interactions and improved therapy adherence to quetiapine when combined with specific co-medications. Yang et al. [41] found no influence of lithium and valproate on the plasma concentration of quetiapine.

#### 3.2.5. Clozapine

The most notable results were found for daily dosage, and the covariates sex, and smoking habit. Linear pharmacokinetics have been noted in numerous studies [22–25], which indicates a dose and serum concentration relationship. Moreover, a positive correlation between female sex and serum concentrations was found in three different studies [22,23,25]. However, another study, with a relatively small sample size, did not identify a relationship between sex and plasma concentrations [26]. Lastly, smoking habits had a negative correlation with exposure of clozapine, which is consistent with the known CYP1A2 induction by tobacco smoke in adults [22,25].

#### 3.2.6. Aripiprazole

Several studies reported linear pharmacokinetics for both aripiprazole and dehydro-aripiprazole [13–17]. Although Rudå et al. [19] did not find a correlation between the serum concentration of aripiprazole and the concomitant use of CYP2D6 inhibitors, their findings showed a significantly higher serum concentration of aripiprazole in CYP2D6 poor metabolizers compared to normal metabolizers. These findings are consistent with those reported by Xin et al. [18]. Age, sex, and weight have also been investigated, but the limited number of results exhibited contradictory findings [13–18]. Finally, no significant correlation with aripiprazole exposure was observed regarding smoking habits [13,14]

## 4. Conclusion

This scoping review presents evidence of the correlations between various covariates and the pharmacokinetics of antipsychotics in the pediatric population. The findings suggest that patient characteristics such as age, sex, weight, smoking habit, co-medication, and CYP2D6 phenotypes can affect the drug serum concentration of commonly used antipsychotics, including risperidone, olanzapine, quetiapine, clozapine, and aripiprazole. Linear pharmacokinetics were noted for most antipsychotics, indicating a linear correlation between dosage and drug exposure. In clinical practice, weight-corrected dosages are commonly used to individualize dosages for each patient. Therefore, the ratio of drug concentration in blood plasma to weight-corrected dosages serves as a valuable parameter in pediatric pharmacokinetic research. However, our findings showed that changes in body weight alone do not fully account for the variability in drug exposure. This stresses the inadequacy of exclusively adjusting dosages

based solely on body weight, emphasizing the necessity of further research to better understand the impact of other covariates along with the implementation of TDM of antipsychotic drugs in the pediatric population.

## 5. Expert opinion

### 5.1. Dosing regimen optimization

Antipsychotic drugs are widely used for treating various psychiatric disorders in pediatric populations. Despite their widespread use, most antipsychotics are prescribed off-label, exhibiting considerable variation in effectiveness across individuals. Additionally, they are associated with potential adverse effects, including weight gain, metabolic abnormalities, cardiac risk, and movement disorders [61–63]. To assist clinicians and pharmacists in determining optimal dosages of antipsychotics for pediatric patients, we have provided a comprehensive overview of significant covariates that can influence the clinical pharmacokinetics of these medications.

Our study's key findings indicate a positive correlation between CYP2D6 phenotype and age with risperidone exposure. The correlation with the CYP2D6 genotype suggests that dosing reductions are needed in the case of reduced CYP2D6 metabolic capacity, as higher risperidone plasma concentrations were found. In the case of the correlation between age and risperidone exposure, we should consider the fact that the majority of the studies did not take the normalization for daily dosage and body weight into account. Therefore, the contribution of age cannot be differentiated. Furthermore, concomitant use of valproate resulted in higher risperidone exposure, suggesting that risperidone dosage should be moderated.

The current evidence regarding the impact of patient characteristics on the pharmacokinetics of olanzapine is inconclusive due to heterogeneous findings. Nevertheless, co-administration with SSRIs has been associated with higher levels of olanzapine, whereas co-administration with valproate has been associated with lower levels. Although the exact mechanism behind these interactions remains unclear, it is recommended to lower dosages of olanzapine when used concomitantly with SSRIs and higher dosages when used with valproate.

For clozapine, female sex has been found to be positively correlated with drug exposure in children and adolescents, indicating that lower dosages of clozapine may be sufficient for females compared to males. Further, smoking habits have a negative correlation with clozapine exposure due to CYP1A2 interaction, which is consistent with findings in adults [64,65]. Therefore, smoking habits should be considered when initiating therapy or adjusting the dosage of clozapine.

Finally, aripiprazole plasma concentration was negatively correlated with CYP2D6 metabolism, while drugs that interact with CYP3A4 significantly affected quetiapine drug concentrations. To conclude, preemptive genotyping may be beneficial in optimizing the dosing of risperidone, quetiapine, and aripiprazole.

### 5.2. Limitations

This review's limitations should be considered when interpreting the findings. Methodologically, the majority of the studies were naturalistic, open-label, observational studies with a relatively small sample size and a short follow-up. Additionally, the studies examining the impact of sex, smoking habits, race, and CYP2D6 phenotypes were often homogeneous, resulting in underpowered subgroups, which limits the ability to detect small effect sizes. Moreover, the existing studies do not comprehensively investigate the impact of puberty-related factors on drug metabolism and treatment outcomes in adolescents. Important aspects, such as potential sex-specific effects, the influence of contraceptive pill use, substance use, dietary habits, concomitant drugs, and lipid mass, are overlooked. To ensure a comprehensive assessment, it is crucial to consider these factors carefully, enabling informed decisions when commencing antipsychotic treatment in children and adolescents. Furthermore, pharmacokinetic outcome measurements were mainly reported as plasma concentration, disregarding the administered dose. Lastly, in many studies, the prescribed daily dosages were not adjusted for weight, which complicates the interpretation of effects related to other potential covariates. By accounting for weight, potential influences arising from developmental changes in body weight and composition would be prevented from being falsely attributed to factors such as age and sex.

### 5.3. Future perspectives

Further research on the relationship between the pharmacokinetic and pharmacodynamic profiles of antipsychotics in pediatric patients is necessary to refine the dosing recommendations extrapolated from the current review. Improvement in our understanding of the impact of covariates on pharmacokinetics and the clinical relevance of the concentration–effect relationship can lead to more precise and individualized dosing strategies.

The available data on the concentration–effect relationship of antipsychotics in children suggest a positive correlation between blood concentrations of risperidone and its active metabolite and clinical response in children with autism spectrum disorder, with higher concentrations associated with increased adverse effects [49]. Similarly, higher plasma concentrations of clozapine were associated with a better clinical response but also an increased risk of adverse effects in children with psychiatric disorders [23]. Additionally, higher plasma concentrations of olanzapine were associated with better treatment response [43]. Despite these meaningful findings, further research is needed to elucidate the concentration–effect relationship, and to define the therapeutic window of antipsychotic drugs in pediatric patients.

The absence of concentration-effect data is a significant challenge for establishing therapeutic reference ranges, which are critical for model-informed precision dosing and implementation of TDM for antipsychotics in pediatric patients. Further research is required to address the impact of TDM for antipsychotics in the pediatric population. Previously, Kloosterboer et al. [66] described this relationship to the extent possible, but a consensus on definitive guidelines for pediatric population has not yet been attained .

By combining individual patient characteristics with TDM, which entails monitoring the drug concentration in the patient's blood and tailoring the dosage accordingly, we can enhance the effectiveness and safety of antipsychotics for each individual.

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## Author contributions

B Koch, B Dierckx and B de Winter: conception and design; R Hermans, J Liang, L Ringeling, and I Bayraktar: abstract screening; J Liang, L Ringeling: analysis, interpretation of the data, and wrote the first and subsequent drafts of the manuscript. All authors discussed the results and gave final approval of the version to be published.

## ORCID

Lisa T. Ringeling http://orcid.org/0000-0002-9354-6429
Sanne M. Kloosterboer http://orcid.org/0000-0003-2573-4636

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