Received: 6 December 2022 | Revised: 7 April 2023 | Accepted: 4 May 2023

DOI: 10.1111/bcp.15800

ORIGINAL ARTICLE

Towards precision dosing of aripiprazole in children and adolescents with autism spectrum disorder: Linking blood levels to weight gain and effectiveness

Rebecca A. Hermans[1,2,3] | Sebastiaan D. T. Sassen[1,3] | Sanne Maartje Kloosterboer[1,2,3] | Catrien G. Reichart[4] | Mirjam E. J. Kouijzer[5] | Matthias M. J. de Kroon[6] | Dennis Bastiaansen[7] | Daphne van Altena[8] | Ron H. N. van Schaik[9] | Kazem Nasserinejad[10] | Manon H. J. Hillegers[2] | Birgit C. P. Koch[1,3] | Bram Dierckx[2] | Brenda C. M. de Winter[1,3]

[1]Department of Hospital Pharmacy, Erasmus Medical Center, Rotterdam, The Netherlands

[2]Department of Child and Adolescent Psychiatry/Psychology, Erasmus Medical Center, Rotterdam, the Netherlands

[3]Rotterdam Clinical Pharmacometrics Group, Erasmus Medical Center, Rotterdam, The Netherlands

[4]LUMC-Curium Child and Adolescent Psychiatry, Leiden University Medical Center, Oegstgeest, The Netherlands

[5]GGz Breburg, Centre of Youth, Breda, the Netherlands

[6]de Kroon Child Psychiatry, Breda, the Netherlands

[7]Yulius Mental Health, Dordrecht, The Netherlands

[8]Department of Youth, GGZ Delfland, Delft, The Netherlands

[9]Department of Clinical Chemistry, Erasmus University Medical Center, Rotterdam, The Netherlands

[10]Department of Hematology, Erasmus Medical Center, Rotterdam, The Netherlands

Correspondence
Birgit Koch, Erasmus University Medical Center Rotterdam, Postbus 2040, 3000 CA. Rotterdam, The Netherlands.
Email: b.koch@erasmusmc.nl

Aims: Aripiprazole is one of the most commonly prescribed antipsychotic drugs to children and adolescents worldwide, but it is associated with serious side-effects, including weight gain. This study assessed the population pharmacokinetics of aripiprazole and its active metabolite and investigated the relationship between pharmacokinetic parameters and body mass index (BMI) in children and adolescents with autism spectrum disorder (ASD) and behavioural problems. Secondary outcomes were metabolic, endocrine, extrapyramidal and cardiac side-effects and drug effectiveness.

Methods: Twenty-four children and adolescents (15 males, 9 females) aged 6–18 years were included in a 24-week prospective observational trial. Drug plasma concentrations, side-effects and drug effectiveness were measured at several time points during follow-up. Relevant pharmacokinetic covariates, including CYP2D6, CYP3A4, CYP3A5 and P-glycoprotein (ABCB1) genotypes, were determined. Non-linear mixed-effects modelling (NONMEM®) was used for a population pharmacokinetic analysis with 92 aripiprazole and 91 dehydro-aripiprazole concentrations. Subsequently, model-based trough concentrations, maximum concentrations and 24-h area under the curves (AUCs) were analysed to predict outcomes using generalized and linear mixed-effects models.

Results: For both aripiprazole and dehydro-aripiprazole, one-compartment models best described the measured concentrations, with albumin and BMI as significant covariates. Of all the pharmacokinetic parameters, higher sum (aripiprazole plus dehydro-aripiprazole) trough concentrations best predicted higher BMI *z*-scores

B. Dierckx and B.C.M. de Winter have contributed equally to this work.

Prof. Dr. Birgit C.P. Koch and Dr. Bram Dierckx are the principal investigators for this study.

Funding information
S.K., B.D. and B.K. received grant research support from The Netherlands Organization for Health Research and Development (ZonMW). R.H. received grant research support from ZonMw and Stichting de Merel.

($P < .001$) and higher Hb1Ac levels ($P = .03$) during follow-up. No significant association was found between sum concentrations and effectiveness.

Conclusions: Our results indicate a threshold with regard to safety, which suggests that therapeutic drug monitoring of aripiprazole could potentially increase safety in children and adolescents with ASD and behavioural problems.

KEYWORDS
antipsychotics, paediatric patients, pharmacometrics, precision dosing, side-effects

1 | INTRODUCTION

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterised by impairments in social communication and interaction, and restricted, repetitive patterns of behaviour.[1] Besides these core symptoms, children with ASD also frequently display irritable and aggressive behaviour.[2] Globally, it is estimated that about 1% of children are diagnosed with ASD.[3] While the core symptoms of ASD can be treated with behavioural and psychoeducational therapy, the associated behavioural problems warrant the use of atypical antipsychotic drugs, like aripiprazole.

Aripiprazole has been proven to significantly reduce ASD-related irritability and aggression in patients, as demonstrated in several randomized controlled trials as well as a meta-analysis.[4] However, the use of atypical antipsychotic drugs is also associated with considerable side-effects, like weight gain, metabolic disturbances, extrapyramidal symptoms (EPS) and sedation.[5] Aripiprazole is often thought to have a more favourable metabolic side-effect profile than other atypical antipsychotic drugs, because of its unique mechanism of action as a partial dopamine D2 receptor agonist. While some studies did indeed find that aripiprazole led to less weight gain than most other atypical antipsychotic drugs,[5,6] weight gain was still found to be significant. A meta-analysis carried out on studies conducted only in children with ASD even found a larger effect size for aripiprazole than for risperidone, albeit with lower absolute weight gain.[4] This results in serious long-term health risks, including metabolic abnormalities and diabetes mellitus.[7,8]

Because of the propensity of aripiprazole to induce side-effects, there is a need for more evidence on its proper and safe use.[9] Dose optimization studies are an important area of research that can contribute to this. In order to optimize dosing, it is important to understand the pharmacokinetics (PK) of aripiprazole in the paediatric population, and how these relate to clinical outcomes (pharmacodynamics, PD). So far, five studies have reported on blood plasma concentrations of aripiprazole in children and adolescents and presented several traditional PK analyses.[10–14] In populations with various psychiatric disorders, they described a linear PK and mostly similar PK parameters to those found in adults. However, none of these studies performed population PK (pop-PK) analyses, an approach with which variability in PK can be quantified and which can be used to correlate PK to PD in order to inform dosing regimens.

What is already known about this subject

- Aripiprazole is a valuable treatment option for autism spectrum disorder related irritability and aggression in children and adolescents, but often causes weight gain and other side-effects.
- While some studies have looked into the pharmacokinetics of aripiprazole in this population, very little is known about the relationship between pharmacokinetic parameters and pharmacodynamic effects.

What this study adds

- Higher sum trough concentrations of aripiprazole and dehydro-aripiprazole correspond to higher body mass index *z*-scores and HbA1c levels.
- We could not find a correlation between aripiprazole plasma trough concentrations and effectiveness.
- Our findings support the role of therapeutic drug monitoring in preventing weight gain caused by aripiprazole, although more research is needed to determine the therapeutic reference range.

While some of the PK studies also reported on clinical outcomes, in only one study was a therapeutic reference range calculated.[11] This yielded a range for children and adolescents with psychotic disorders that was comparable to the therapeutic reference range for adults, and slightly lower limits when all diagnoses were included. However, the researchers used a rough estimation method, which did not take into account side-effects, levels of the active metabolite dehydro-aripiprazole, or other covariates apart from diagnosis.

The objective of our current research is twofold. First, we aim to correlate aripiprazole and dehydro-aripiprazole blood concentrations, obtained using pop-PK analyses, to weight gain, other side-effects and therapy effectiveness in children and adolescents with ASD and

comorbid irritability and aggression. Secondly, using this correlation, a therapeutic window will be determined, which could be used to improve care for these patients through therapeutic drug monitoring.

2 | METHODS

2.1 | Study population

Participants were enrolled in a 24-week observational prospective multicentre cohort study (Netherlands Trial Register 6050). Inclusion criteria were: age 6–18 years, a diagnosis of ASD according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) IV[15] or 5[1] with comorbid behavioural problems, and use or initiation of treatment with aripiprazole. Patients with diabetes type I or II, congenital or acquired syndromes associated with changes in appetite, body weight or lipid profile (e.g. Prader Willi), treatment with another antipsychotic drug within the last 6 months, and known long QT syndrome were excluded. Recruitment took place between August 2016 and October 2018 in six centres in the Netherlands (two academic tertiary care centres and four psychiatric secondary care centres). Patients were prescribed aripiprazole as tablet formulation or oral solution in flexible dosing schemes by their treating physician according to standard clinical care. Written informed consent was obtained from patients and/or their legal representatives. The study was approved by the medical ethics committee of the Erasmus Medical Center, the Netherlands (number MEC 2016-124) and was carried out in accordance with the Declaration of Helsinki and the Regulations on Medical Research with Human Subjects, the Netherlands.

2.2 | Drug concentration measurements

A total of six blood samples per patient were collected for aripiprazole and dehydro-aripiprazole quantification at random time points, with at least 1 h between two samples, and on two separate days. Sampling occurred at 12 and 24 weeks after baseline for aripiprazole naive patients, and at baseline and at 24 weeks after baseline for non-aripiprazole-naive patients. Blood was sampled using venepuncture or the dried blood spot (DBS) method via fingerpick. Time of sampling, aripiprazole dose and time of intake in the prior 24 h, and comedication were reported during sampling. Aripiprazole and dehydro-aripiprazole plasma concentrations were measured using a validated ultrahigh performance liquid chromatography-tandem mass spectrometry (LC–MS/MS) method for plasma and DBS.[16–18] The lower limit of quantification (LLOQ) was 10 μg/L for both aripiprazole and dehydro-aripiprazole in plasma as well as DBS. The lower limit of detection (LOD) was 0.60 μg/L in plasma and 10 μg/L in DBS for aripiprazole, and 1.8 μg/L in plasma and 0.7 μg/L in DBS for dehydro-aripiprazole.

DBS concentrations (DBS_{conc}) were converted with correction for haematocrit (ht) based on a previously conducted clinical validation study to estimated plasma concentrations (EPC)[16] using the following formulas:

$$EPC_{aripiprazole} = (DBS_{conc}/[1 - ht])/1.263$$

$$EPC_{dehydro-aripiprazole} = (DBS_{conc}/[1 - ht])/1.242$$

Haematocrit was measured in blood sampled through venepuncture. When venepuncture had not been performed and extrapolation from a previous measurement was not possible, the median population value was used.

2.3 | Assessment of outcomes

Side-effects and effectiveness were prospectively recorded at baseline and at 24 weeks after baseline for all patients. Aripiprazole-naive patients were also assessed for side-effects and effectiveness at 4 and 12 weeks after baseline. For non-aripiprazole-naive patients, bodyweight, height, laboratory measurements and comedication since initiation of aripiprazole were retrospectively collected from the patient file.

2.3.1 | Side-effects

Bodyweight and height were measured at each visit. The Abnormal Involuntary Movement Scale (AIMS)[19] was used to measure EPS by the treating physician, nurse or researcher. Sedation was assessed by parents using the Epworth Sleepiness Scale.[20] Triglycerides, total cholesterol, high-density lipoprotein (HDL)-cholesterol, low-density lipoprotein (LDL)-cholesterol, glucose, haemoglobin A1c (HbA1c) and prolactin were measured at baseline and at 24 weeks after baseline, with an additional measurement at 12 weeks for aripiprazole-naive patients.

QT intervals were measured in triplicate from a 12-lead ECG and converted to QTc as described previously[21] at baseline and at 24 weeks after baseline. The QT times and RR intervals were measured by a researcher and in case of doubt also reviewed by an experienced paediatric cardiologist.

2.3.2 | Effectiveness

Treatment effectiveness was assessed by both parents and the treating physician. Parents filled in the Aberrant Behavior Checklist (ABC),[22] a 58-item questionnaire from which the irritability subscale (ABC-I) was used as measure of effectiveness. On the ABC-I, irritability symptoms are rated with a maximum of 45 points. Treating physicians filled in the Clinical Global Impression Scale (CGI),[19] of which the severity scale (CGI-S) was used. The CGI-S describes the severity of psychopathology relative to patients with the same diagnosis by seven categories in ascending order, with 1, *Normal* and 7, *Extremely ill*.

2.4 | Assessment of covariates

Information on comedication was extracted from medical and pharmacy records. Methylphenidate, amphetamine and atomoxetine were grouped together as comedication for attention deficit/hyperactivity disorder (ADHD). Information on psychiatric as well as somatic comorbidities was gathered at baseline. Familial cardiometabolic risk, as previously defined by the American Academy of Pediatrics,[23] was assessed after taking the family history at baseline. If family history was unknown, it was considered positive for cardiometabolic risk.

Renal function (urea, creatinine), liver function (aspartate aminotransferase [ASAT], alanine aminotransferase [ALAT], gamma glutamyl transpeptidase [GGT], alkaline phosphatase [AP] and albumin) and haematocrit were assessed at baseline and during follow-up.

Genotyping: Genomic DNA was isolated from 200-μL ethylenediaminetetraacetic acid (EDTA) whole blood using a MagNA Pure Compac (Roche Diagnostics GmbH, Mannheim, Germany). Genotyping was performed for *CYP2D6*3* (2549delA, rs35742686), **4* (1846G>A, rs3892097), **5* (gene deletion) and **41* (2988G>A, rs28371725), *ABCB1* 3435C>T (rs1045642), *CYP3A4*22* (g.15389C>T, rs35599367), *CYP3A5*3* (6986A>G, rs4986910) and **6* (14690G>A, rs10264272). Analyses were performed using Taqman 5′ nuclease DME assays (ThermoFisher Scientific, Carlsbad, CA, USA). All pharmacogenetic analyses were performed at the Department of Clinical Chemistry of Erasmus MC, Rotterdam, the Netherlands.

2.5 | Population pharmacokinetic analyses

Population pharmacokinetic analysis was performed by nonlinear mixed-effects modelling using NONMEM version 7.4.4 (FOCE+I; ICON Development Solutions, Ellicott City, MD, USA) and PsN Version 4.7.0. Pirana software version 2.9.7 was used as an interface between NONMEM and R (version 4.1.3). Concentrations of aripiprazole and dehydro-aripiprazole were converted from μg/L to nmol/L to correct for differences in molecular weight.

2.5.1 | Model development

Initially, a one-compartment model with first-order absorption was fitted to the aripiprazole concentration–time data. Typical values for first-order absorption rate constant (Ka), volume of distribution (V), and clearance (CL) were estimated. As bioavailability (F) could not be assessed, apparent CL and V were estimated (CL/F and V/F). Subsequently, more complex models were evaluated. Allometric scaling to a bodyweight of 70 kg was implemented a priori. Models with fixed exponent values of 0.75 for flow-dependent process parameters and 1 for volume-related parameters, which are the standard exponent values,[24–26] were compared to models with estimated exponent values. The models were evaluated and compared both numerically (e.g. [delta] objective function value ([d]OFV), parameter estimations, precision, shrinkage[27] and conditional number) and visually (using goodness-of-fit [GoF] plots and visual predictive checks [VPCs]). First, aripiprazole data were described and subsequently dehydro-aripiprazole data were added. For each PK parameter, interindividual variability (IIV) was estimated using an exponential model. Residual variability was tested with additive, proportional and combined (additive and proportional) error models, with an extra error for sampling method (DBS *vs.* venepuncture). A decrease in the OFV of >3.84 points for a nested model with one degree of freedom was considered statistically significant ($P < .05$). Finally, all available covariates were evaluated using iterative forward selection ($P < .05$) and iterative backward elimination ($P < .01$). Continuous covariates were described using an exponential function centred around the median and categorical covariates using a proportional function.

2.5.2 | Model validation

First, the robustness of the model parameter estimates was evaluated using a non-parametric bootstrap procedure ($n = 1000$).[28] The bootstrap estimates and their 90th percentile range were compared with the estimates from the original dataset. Second, the model was evaluated with VPCs stratified for aripiprazole and dehydro-aripiprazole, using a set of 1000 simulated datasets to compare the observed concentrations with the distribution of the simulated concentrations.[29]

2.5.3 | Pharmacokinetic predictions

For the days on which weight and height were measured (and thus a BMI *z*-score could be calculated), we calculated C_{trough} and AUC_{24h} of aripiprazole, dehydro-aripiprazole and the sum of these two compounds using model-based individual PK predictions. The C_{trough} prior to the first aripiprazole administration of the day was used.

2.6 | Pharmacodynamic analyses

Correlation between calculated C_{trough} and AUC_{24h} of aripiprazole, dehydro-aripiprazole, and their sum and outcome was assessed in the PD analyses. Each of these PK predictions was separately analysed as predictor for BMI *z*-score.

2.6.1 | Primary outcome

The primary outcome was the BMI *z*-score: BMI adjusted for age and gender based on the World Health Organization's (WHO) BMI-for-age reference values (5–19 years).[30] The WHO classifies a BMI *z*-score of ≥1 as overweight and a BMI *z*-score of ≥2 as obesity. For establishment of a therapeutic reference range, we adhered to the clinical consensus that a 5% change in bodyweight is clinically relevant.[31] An additional 5% gain of bodyweight on top of a child's normal growth trajectory corresponds with an increase of about 0.5 in BMI *z*-score in 6 months.

2.6.2 | Secondary outcomes

As secondary outcomes ABC-I score, CGI-S score, EPS, sedation, triglyceride level, total cholesterol level, HDL-cholesterol level, LDL-cholesterol level, glucose level, HbA1C level, prolactin level and QTc time were assessed. EPS, sedation and CGI-S were considered categorical outcomes. A patient was considered positive for EPS if at least two items were scored as mild or one item as moderate on the AIMS, and for sedation if the total score on the ESS was 1 or higher. Patients were only included in the analyses if there was a measurement of the concerning outcome taken before start of aripiprazole treatment.

2.7 | Statistical analyses for correlation between concentration and effect

For the primary outcome, the longitudinal data were analysed with generalized and linear mixed-effects models. Heterogeneity between patients was assessed with random effects. Potentially relevant covariates were tested in each model and the best model was selected using backwards variable selection. The final model was chosen from among all the best models with different PK predictions of aripiprazole based on the Akaike information criterion (AIC).[32]

The secondary analyses were performed with the PK prediction (e.g. AUC aripiprazole) that was selected for the primary outcome. This PK prediction was entered as predictor in univariable models and, if significant, covariates were added in a stepwise manner. Correlations between model-based PK predictions were analysed with Pearson's correlation. Changes in BMI *z*-scores between start of medication and 6 months was assessed with a paired samples *t*-test. In all analyses, $P < .05$ was considered significant. Generalized and linear mixed-effects modelling was performed in R (version 4.1.3), the other analyses in SPSS (version 28.0.1.0).

3 | RESULTS

3.1 | Study sample

Twenty-four children were enrolled in the study. However, one participant had to be excluded from analyses, because the only measured drug levels were sampled 4 days after last medication intake. Of the remaining 23 participants, 17 were aripiprazole-naive.

See Table 1 for patient characteristics. Eleven children (47.8%) had one or more comorbid psychiatric disorders besides ASD, namely ADHD (47.8%), anxiety disorder (8.7%) and oppositional defiant disorder (ODD, 4.3%).

Dosages used during the entire study period ranged from 0.5 to 6 mg, in one or two doses a day. Fifty-eight DBS samples and 34 plasma samples were obtained at a median time after dose of 3.35 h (range 0.43–25 h). The median (IQR) measured/estimated plasma concentrations of aripiprazole were 57.32 (38.7) μg/L in venepuncture and 34.78 (46.62) μg/L in DBS. The median (IQR) measured/estimated plasma concentrations of dehydro-aripiprazole were 18.07 (11.18) μg/L in venepuncture and 12.89 (12.89) μg/L in DBS.

3.2 | Population pharmacokinetic analyses

A one-compartment model with application of allometric scaling (with fixed exponents 0.75 for CL and 1 for V) best described the data for both aripiprazole and dehydro-aripiprazole. Separate proportional errors for DBS and venepuncture were used to describe the residual error. The model improved significantly by adding interindividual variability (IIV) for V and CL of aripiprazole, and for CL of dehydro-aripiprazole.

In a univariate covariate analysis, albumin and BMI were significant covariates for CL of aripiprazole. After forward inclusion and backward elimination, both were included as covariates in the final model. Albumin showed a positive correlation, and BMI a negative correlation. Together, they explained 49.3% of the IIV of CL of aripiprazole. Because of poor precision, we decided to fix Ka at 1.72 h^{-1}, the value estimated by the final model. This corresponds to an approximate T_{max} of 1.2 h, which falls within the ranges previously described in children and adolescents.[12,13] All evaluations of the final model were good, except for a higher shrinkage of 34% for IIV on V aripiprazole, which was accepted. Goodness-of-fit plots showed a good ability of the model to describe the observed concentrations (Figure S1a, S1b). Estimates of the base and final models are shown in Table 2. See Figure 1 for a visual representation of the relationship between CL of aripiprazole and its covariates. This figure shows albumin has the biggest effect on CL, while BMI *z*-score only marginally changes CL.

The model was successfully validated using bootstrap analysis (Table 2). VPCs confirmed that the model adequately predicts concentrations across 24 h after dose for aripiprazole (Figure S2). A diagram of the model can be found in Figure S3.

For the time points for which a BMI *z*-score was known, model-based individual PK predictions were calculated for C_{trough} and AUC_{24h} of aripiprazole, dehydro-aripiprazole and their sum.

3.3 | Pharmacodynamic analyses

3.3.1 | Primary outcome: BMI *z*-scores

For four patients (all non-aripiprazole-naive), bodyweight and height at initiation of treatment were not known. For the remaining 19 patients, a total of 86 BMI *z*-scores could be calculated. In the 16 participants for whom BMI *z*-scores were known at both start of treatment and 6 months after start of treatment, mean BMI *z*-scores increased from 0.53 (±1.33) to 0.60 (±1.31). This increase was not significant ($P = .331$).

Higher extrapolated C_{trough} and AUC_{24} levels for aripiprazole, dehydro-aripiprazole and their sum, all significantly predicted higher

TABLE 1 Patient characteristics.

Characteristic		n
Male, *n* (%)	15 (65)	23
Age[a] (years)	9.55 (5.08)	23
Bodyweight[a] (kg)	35.5 (31.5)	19
Height[a] (m)	1.4 (0.31)	19
Body mass index[a] (kg/m^2)	18.06 (3.89)	19
Body mass index *z*-score[a]	0.92 (1.94)	19
Aripiprazole daily dose[a] (mg)	1 (1.5)	23
Both parents Dutch[b], *n* (%)	18 (78.3)	23
Laboratory measurements[a,c]		
Triglycerides (mmol/L)	0.72 (0.47)	14
Total cholesterol (mmol/L)	4 (0.9)	15
HDL cholesterol (mmol/L)	1.4 (0.6)	15
LDL cholesterol (mmol/L)	2.4 (1.03)	14
Glucose (mmol/L)	4.95 (0.45)	14
HbA1c (mmol/Mol)	34 (3)	11
Prolactin (U/L)	0.15 (0.35)	9
Albumin	43.5 (3.5)	16
Genotype, *n* (%)		23
CYP2D6		
Poor metabolizer	2 (8.7)	
Intermediate metabolizer	12 (52.2)	
Normal metabolizer	7 (30.4)	
CYP3A4		
Poor metabolizer	0	
Intermediate metabolizer	1 (4.3)	
Normal metabolizer	20 (87.0)	
CYP3A5		
Expressor	5 (21.7)	
Non-expressor	12 (52.2)	
ABCB1		
Poor metabolizer	4 (17.4)	
Intermediate metabolizer	1 (4.3)	
Normal metabolizer	14 (60.9)	
QTc time (ms)[a]	373 (38)	11
Clinical Global Impression scale (CGI-s) score[a]	5 (1)	17
Aberrant Behavior Checklist – Irritability scale[a]	17 (8.75)	14
Comorbid psychiatric disorders other than ASD, *n* (%)	11 (47.8%)	23
Comedication ADHD drugs[c,d], *n* (%)	5 (21.7)	23
IQ[a]	85 (9)	11
Prior psychotropic treatment, *n* (%)	19 (82.6)	23
Increased familial cardiometabolic risk, *n* (%)	5 (21.7)	
Formulation of aripiprazole, *n* (%)		23
Tablet	22 (95.7)	
Oral solution	1 (4.3)	

Note: The values represent start of aripiprazole treatment unless otherwise specified.
Abbreviations: ADHD, attention deficit/hyperactivity disorder; ASD, autism spectrum disorder; CYP, cytochrome P450; HbA1C, haemoglobin A1C; HDL, high-density lipoprotein; LDL, low-density lipoproteins; PGP, P-glycoprotein; QTc, corrected QT.
[a]Median (IQR).
[b]Four children had one or two parents of non-European descent.
[c]Values represent baseline measurement of study.
[d]Includes methylphenidate, amphetamine, atomoxetine.

TABLE 2 Pharmacokinetic parameter estimates of the base model, final model and bootstrap analysis.

Parameter	Base model estimate (SE)	Final estimate (SE)	Bootstrap median (90th percentile)
Aripiprazole			
Ka[a] h^{-1}	2.28 (2.1)	1.72 (FIX)	1.72
V/F[b] L/70 kg	210 (56.9)	196 (50.9)	195 (117–340)
– IIV	103.8%	85.9%	81.5% (30.4–161.4)
CL/F[b] L/h/70 kg	4.15 (0.48)	4.41 (0.41)	4.41 (3.59–5.37)
– IIV	45.3%	31.5%	28.3% (14.8–35.8)
– Albumin		2.11 (0.74)	2.15 (0.58–3.85)
– BMI		−1.01 (0.38)	−1.02 (−1.73–0.13)
Dehydro-aripiprazole			
V/F[b] L/70 kg	23.4 (6.71)	22.6 (7.04)	22.4 (2.97–206)
CL/F[b] L/h/70 kg	12.1 (1.31)	12.2 (1.33)	12.3 (9.81–15.3)
– IIV	44.5%	45.6%	43.5% (26.7–58.5)
Proportional errors			
Plasma	0.38 (0.09)	0.41 (0.07)	0.40 (0.21–0.57)
DBS	0.22 (0.03)	0.21 (0.02)	0.21 (0.16–0.27)

Note: F represents bioavailability for aripiprazole parameters, or the fraction metabolized to dehydro-aripiprazole for the dehydro-aripiprazole parameters. Bootstrap analyses: calculated based on 874 of the 1000 runs which were successful. $CL_{aripiprazole} = 4.41*(bodyweight/70)^{0.75}*(Albumin/45)^{2.11}*(BMI/18.51)^{-1.01}$. Bootstrap analyses: calculated based on 874 of the 1000 runs which were successful. $CL_{aripiprazole} = 4.41*(bodyweight/70)^{0.75}*(Albumin/45)^{2.11}*(BMI/18.51)^{-1.01}$.

[a]Fixed value.

[b]Allometric scaling with exponent 1 for V, and 0.75 for CL.

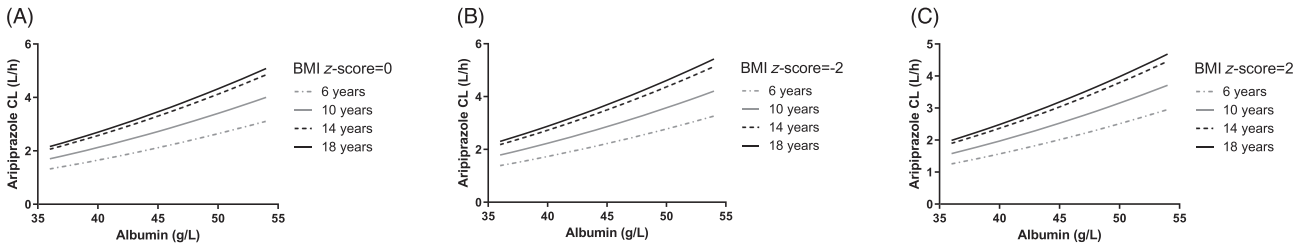

FIGURE 1 Relationship between albumin and clearance of aripiprazole at different BMI *z*-values. The relationship between albumin and the population value for aripiprazole clearance (CL) is presented for different age levels and corresponding mean weight and BMI values, for children with BMI *z*-score = 0 (A), BMI *z*-score = −2 (B) and BMI *z*-score = 2 (C).

BMI *z*-scores during follow-up. Female sex was a covariate in multivariate analyses, predicting lower BMI *z*-scores.

AICs for the models using C_{trough} of aripiprazole, C_{trough} of the sum of aripiprazole and dehydro-aripirazole and AUC_{24} of aripiprazole differed by less than 2. This means that these four models are essentially indistinguishable. Based on the same analyses previously performed for risperidone[33] and on clinical usability, we decided on the model for sum C_{trough} as the final model, with female sex as covariate (Table 3).

3.3.2 | Secondary outcomes

No significant association was found between sum C_{trough} and ABC-irritability scores or response on the CGI-S. Sum C_{trough} did, however, significantly predict HbA1c levels ($P = .03$). No significant association was found between sum C_{trough} and the other secondary side-effect markers. The results of the effectiveness analyses are presented in Table 3 and of the secondary side-effects analyses in Table S1.

3.3.3 | Therapeutic reference range

Based on our model, a sum C_{trough} level of 59.6 µg/L or higher will lead to an increase in BMI *z*-score of 0.5 or higher, $t(39) = 3.60$, $P < .001$. This value could be used as an upper cut-off value (Figure 2). Because we found no significant association between sum C_{trough} and effectiveness, it is not possible to calculate a lower cut-off value for a therapeutic window. The lowest sum C_{trough} level with which a patient

TABLE 3 Association between trough concentrations of aripiprazole + dehydro-aripiprazole and primary and secondary outcomes.

Variable	*n* (obs)	Estimate	Standard error	ICC	*P*-value
Primary outcome					
BMI *z*-score	19 (56)			0.95	
β0		0.689	0.356		.068
Sum C_{trough} (μg/L)		0.008	0.002		<.001**
Female sex		−0.997	0.571		.099
Secondary outcomes effectiveness					
CGI – response	17 (45)			–	
β0		1.866	0.963		.053
Sum C_{trough} (μg/L)		0.001	0.015		.925
Female sex		−2.31	0.909		.011*
ABC – irritability	14 (26)			0.73	
β0		11.144	3.469		.004*
Sum C_{trough} (μg/L)		−0.006	0.038		.867
ADHD comedication		10.155	4.679		.046*

Note: Example equation of the relationships analysed. BMI *z*-score = 0.689 + Sum C_{trough} * 0.008–0.997 (if female); while change in BMI *z*-score 6 months after start of treatment = Sum $C_{trough\ 6mths}$ * 0.008.
Abbreviations: ABC, Aberrant Behavior Checklist; CGI, Clinical Global Impression Scale, ICC, Intraclass correlation coefficient.
*P < .05. **P < .001.

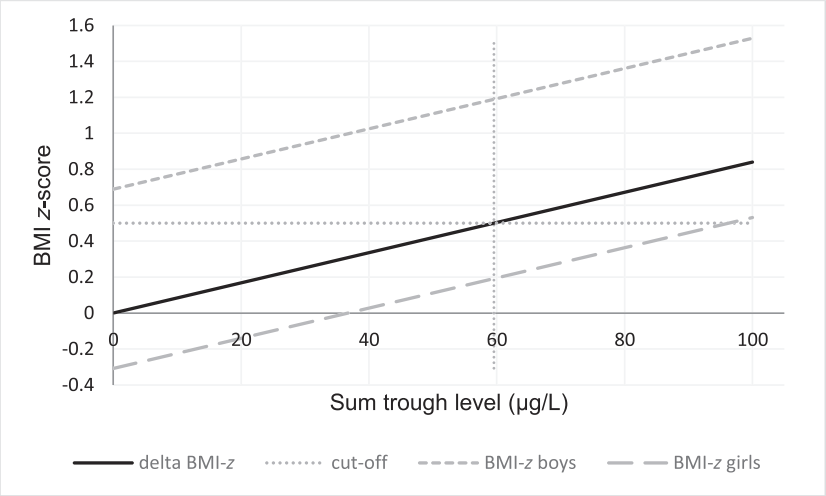

FIGURE 2 Upper cut-off value for sum C_{trough} based on change in BMI *z*-score, plus BMI *z*-score at 6 months for the male and female subjects in our study. On the horizontal axis the sum trough plasma concentration in μg/L. On the vertical axis the BMI *z*-score after 6 months.

achieved sufficient treatment effect (defined as ≥ 25% reduction on the ABC-I) was 13.6 μg/L. This value can be used to inform a decision on a preliminary lower cut-off value.

4 | DISCUSSION

This is the first study to build a pop-PK model for aripiprazole in children and adolescents and to correlate PK parameters with both side-effects and clinical effectiveness. A one-compartment PK model for both aripiprazole and dehydro-aripiprazole best described our data. We found a positive correlation of sum C_{trough} plasma levels with weight gain as well as HbA1c, but not with effectiveness.

Pharmacokinetic parameters in adult pop-PK models for aripiprazole show quite some variability, but the parameters we found fall within the ranges these models describe.[34] In addition, we found similar values for CL and T_{max} as previously described in children and adolescents.[13] In other manuscripts significant covariates found are CYP2D6 on CL in adults[35–38]; in children, number of concomitant drugs,[14] age and gender[11] are cited as possibly having an influence on aripiprazole blood levels. Except for an effect of female sex, we did not find these associations. Maybe, our sample size was too small to notice these differences, as we, for example, only had two poor metabolizers for CYP2D6 in our group.

A surprising result from the PK analysis was the positive correlation between albumin and CL of aripiprazole. Albumin was a relevant

covariate to consider in our analysis, because it extensively binds both aripiprazole and dehydro-aripiprazole.[39] Graphical analysis of the relationship between CL, BMI and albumin shows that albumin is a relevant laboratory value to measure in order to be able to properly calculate model-based plasma concentrations. Higher albumin values were found to increase clearance. However, based on the binding property and expected kinetics relationships, the expected correlation with CL would be the other way round, as only the unbound fraction can be cleared. Our contrary finding suggests that albumin is most likely a surrogate for another covariate which we did not analyse. We have observed this before, when it was a surrogate for wellbeing or frailty.[40] We find it difficult to link this to our population, as we did not observe malnourished children or adolescents.

The relationship between PK and bodyweight is complicated. Both body weight (using allometric scaling) and BMI are covariates in the PK model. Incorporation of allometric scaling shows that higher body weight will lead to an increased V and CL, resulting in lower plasma levels. However, we also found that a higher BMI leads to lower CL and higher plasma levels. This seems counterintuitive. A possible explanation is that age or height play a role in this association and that the correlation between weight and clearance (via allometric scaling) is not straightforward. As aripiprazole is highly lipophilic, with increased body weight, increased V and CL would be expected. In adults, weight has been found to be a positive covariate for CL[37,38] and V.[35,37,38] It seems that this covariate is not that straightforward in children and adolescents and both allometric scaling via a positive factor and BMI as a negative factor show this association in our population. A possible explanation would be the following: with less increase in CL in comparison to V with regard to weight, it seems that the negative relation between BMI and CL is therefore the correction for the extra weight gain caused by using antipsychotics in comparison to normal maturation of children (via allometric scaling).

With regard to pharmacodynamics, we found that higher sum trough levels of aripiprazole and dehydro-aripiprazole predicted higher BMI *z*-scores (difference in BMI). This is the first study to have analysed this relationship. Surprisingly, there was no overall significant increase in BMI *z*-score in our study population. Considering the large body of evidence on weight gain caused by aripiprazole in children and adolescents,[4–6] this is likely the result of our small sample size and the relatively low dosages of aripiprazole prescribed to the participants in this study. If we exclude the outlier in our BMI *z*-score data (a participant who saw a dietician throughout the entire study period and lost 12.4 kg, leading to a change in BMI *z*-score of −1.47), BMI *z*-score increased from 0.50 (±1.37) to 0.67 (±1.33). This decreases the *P*-value to .091. This could also be a confounder by indication, as children with a higher baseline body weight will be more prone to start with aripiprazole. Importantly, the lack of overall increase in BMI *z*-score does not negate the correlation with aripiprazole concentrations.

We also established a positive correlation between aripiprazole sum trough levels and HbA1c. The other research linking drug plasma levels to HbA1c was performed in adults, where, counterintuitively, non-significantly lower HbA1c values were found among patients using a higher dosage of aripiprazole.[41] Other studies, such as Castilla-Puentes, found the same result as us, linking an increase in HbA1c to use of antipsychotics.[42] In addition, Nicol et al. observed an increased insulin resistance within 12 weeks of antipsychotic use.[43] It has been proposed that atypical antipsychotics may contribute directly to type 2 diabetes by inhibiting cellular glucose uptake. A recent study reported that antipsychotics may do so by blocking the glucose transporter protein in cell membranes.[44] Contradictory results may be related to other factors such as limitations of the studies performed and more research is needed to confirm the association.

According to our findings, adhering to a maximum sum C_{trough} level of 59.6 μg/L may be able to limit weight gain. No clear lower cut-off value can yet be defined, as we did not find an association between higher levels of aripiprazole and increased effectiveness. This warrants further research in larger studies. However, a minimum value is not imperative for therapeutic drug monitoring to have clinical benefit.

Our findings lead to a considerably lower upper cut-off value than in the only previously proposed therapeutic window for aripiprazole in the paediatric population.[11] This therapeutic window for children and adolescents with all psychiatric diagnoses was proposed at aripiprazole plasma levels of 60.7–372.1 μg/L to have an improvement in CGI (effect). Because our results are based on sum levels of aripiprazole and dehydro-aripiprazole instead of solely on aripiprazole levels, the true difference in suggested limits is even greater than at first glance. However, this study found higher cut-off values (105–375.3 μg/L) when only taking patients with psychotic disorders into account, which suggests that there are different therapeutic reference ranges for different treatment indications. It is thus very well possible that the reference range for ASD-related irritability in their sample would be closer to the results of our study. This finding only confirms the need for precision dosing using pharmacometrics which are targeted to specific populations.

Another unexpected result was that we found a smaller proportional error for DBS samples than for plasma samples. Due to smaller precision and the need to convert DBS measurements to EPCs, the contrary would be expected, as was found in a previous study.[33] This is a nice observation for the precision of DBS in these children.

The results of this study should be considered in the light of its limitations. First, we had a small sample size. For the PK analysis, this led to an unstable model, with poor precision for either Ka or for V of dehydro-aripiprazole. Along with the small number of samples taken in the absorption phase, this led to the decision to fix the estimate of Ka. From our already small participant sample, only a subset could be included in the PD analyses, which has possibly led to nonsignificant results on correlations between sum trough levels and effectiveness as well as secondary safety parameters. Inclusion of all recorded data, including outliers, can be considered a strength of our study, as this leads to a more honest representation of the clinical setting. What could be considered as a second limitation is that we made use of model-based levels instead of measured plasma levels in our PD analyses. However, our method allowed us to determine levels at precisely 24 h after dose. Sampling at such precise times would not

have been possible, especially with outpatient participants. Third, we made use of drug levels measured in both plasma and DBS, which led to greater variability in measured and model-based concentrations. In order to minimize this variability, we have included the different sampling methods in our error model. Moreover, including both methods allowed for more frequent sampling than would have been possible with venepuncture alone, and helped research the feasibility of DBS as a sampling method for clinical practice.

5 | CONCLUSION

This is the first study that researched the relationship between aripiprazole PK, side-effects and effectiveness in the paediatric population. The correlation we found between higher plasma levels and a higher amount of weight gain suggests that there is a role for therapeutic drug monitoring in optimizing care and warrants further research. The clinical benefit of therapeutic drug monitoring of aripiprazole in this population will be investigated in a follow-up randomized controlled trial.

AUTHOR CONTRIBUTIONS

Birgit C. P. Koch and Bram Dierckx took first responsibility for initiating the trial and applying for funding. Sanne Maartje Kloosterboer, Brenda C. M. de Winter, Manon H. J. Hillegers, Birgit C. P. Koch and Bram Dierckx contributed to the conception of the study protocol and study design. Sanne Maartje Kloosterboer was coordinating researcher. Catrien G. Reichart, Mirjam E. J. Kouijzer, Matthias M. J. de Kroon, Dennis Bastiaansen and Daphne van Altena were responsible for data collection in their respective centers. Ron H. N. van Schaik was responsible for pharmacogenetic testing. Sebastiaan D. T. Sassen and Kazem Nasserinejad performed PK and PD analyses, respectively. Rebecca A. Hermans performed PK and PD analyses and wrote the first draft of the manuscript. All authors contributed to subsequent drafts and gave final approval of the version to be published.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Rebecca A. Hermans https://orcid.org/0000-0001-9622-2246
Sanne Maartje Kloosterboer https://orcid.org/0000-0003-2573-4636
Kazem Nasserinejad https://orcid.org/0000-0002-5666-5015
Birgit C. P. Koch https://orcid.org/0000-0002-1202-3643

REFERENCES

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed; 2013. doi:10.1176/appi.books.9780890425596
2. Lecavalier L. Behavioral and emotional problems in young people with pervasive developmental disorders: relative prevalence, effects of subject characteristics, and empirical classification. *J Autism Dev Disord*. 2006;36(8):1101-1114. doi:10.1007/s10803-006-0147-5
3. Zeidan J, Fombonne E, Scorah J, et al. Global prevalence of autism: a systematic review update. *Autism Res*. 2022;15(5):778-790. doi:10.1002/aur.2696
4. Fung LK, Mahajan R, Nozzolillo A, et al. Pharmacologic treatment of severe irritability and problem behaviors in autism: a systematic review and meta-analysis. *Pediatrics*. 2016;137(Suppl 2):S124-S135. doi:10.1542/peds.2015-2851K
5. Cohen D, Bonnot O, Bodeau N, Consoli A, Laurent C. Adverse effects of second-generation antipsychotics in children and adolescents: a Bayesian meta-analysis. *J Clin Psychopharmacol*. 2012;32(3):309-316. doi:10.1097/JCP.0b013e3182549259
6. De Hert M, Dobbelaere M, Sheridan EM, Cohen D, Correll CU. Metabolic and endocrine adverse effects of second-generation antipsychotics in children and adolescents: a systematic review of randomized, placebo controlled trials and guidelines for clinical practice. *Eur Psychiatry*. 2011;26(3):144-158. doi:10.1016/j.eurpsy.2010.09.011
7. Calarge CA, Acion L, Kuperman S, Tansey M, Schlechte JA. Weight gain and metabolic abnormalities during extended risperidone treatment in children and adolescents. *J Child Adolesc Psychopharmacol*. 2009;19(2):101-109. doi:10.1089/cap.2008.007
8. Bobo WV, Cooper WO, Stein CM, et al. Antipsychotics and the risk of type 2 diabetes mellitus in children and youth. *JAMA Psychiatry*. 2013;70(10):1067-1075. doi:10.1001/jamapsychiatry.2013.2053
9. Rafaniello C, Sullo MG, Carnovale C, et al. We really need clear guidelines and recommendations for safer and proper use of aripiprazole and risperidone in a pediatric population: real-world analysis of EudraVigilance database. *Front Psych*. 2020;11:550201. doi:10.3389/fpsyt.2020.550201
10. Bachmann CJ, Rieger-Gies A, Heinzel-Gutenbrunner M, Hiemke C, Remschmidt H, Theisen FM. Large variability of aripiprazole and dehydroaripiprazole serum concentrations in adolescent patients with schizophrenia. *Ther Drug Monit*. 2008;30(4):462-466. doi:10.1097/FTD.0b013e318178e18d
11. Egberts K, Reuter-Dang SY, Fekete S, et al. Therapeutic drug monitoring of children and adolescents treated with aripiprazole: observational results from routine patient care. *J Neural Transm (Vienna)*. 2020;127(12):1663-1674. doi:10.1007/s00702-020-02253-4
12. Findling RL, Kauffman R, Sallee FR, et al. An open-label study of aripiprazole: pharmacokinetics, tolerability, and effectiveness in children and adolescents with conduct disorder. *J Child Adolesc Psychopharmacol*. 2009;19(4):431-439. doi:10.1089/cap.2008.0111
13. Findling RL, Kauffman RE, Sallee FR, et al. Tolerability and pharmacokinetics of aripiprazole in children and adolescents with psychiatric disorders: an open-label, dose-escalation study. *J Clin Psychopharmacol*. 2008;28(4):441-446. doi:10.1097/JCP.0b013e31817dd520
14. Pozzi M, Cattaneo D, Baldelli S, et al. Therapeutic drug monitoring of second-generation antipsychotics in pediatric patients: an observational study in real-life settings. *Eur J Clin Pharmacol*. 2016;72(3):285-293. doi:10.1007/s00228-015-1982-0
15. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed; 2000.
16. Kloosterboer SM, de Winter BCM, Bahmany S, et al. Dried blood spot analysis for therapeutic drug monitoring of antipsychotics: drawbacks of its clinical application. *Ther Drug Monit*. 2018;40(3):344-350. doi:10.1097/FTD.0000000000000502
17. Tron C, Kloosterboer SM, van der Nagel BCH, et al. Dried blood spots combined with ultra-high-performance liquid chromatography-mass spectrometry for the quantification of the antipsychotics risperidone, aripiprazole, pipamperone, and their major metabolites. *Ther Drug Monit*. 2017;39(4):429-440. doi:10.1097/FTD.0000000000000411

18. Wijma RA, van der Nagel BC, Dierckx B, et al. Identification and quantification of the antipsychotics risperidone, aripiprazole, pipamperone and their major metabolites in plasma using ultra-high performance liquid chromatography-mass spectrometry. *Biomed Chromatogr*. 2016; 30(6):794-801. doi:10.1002/bmc.3610
19. Guy W. *ECDEU Assessment Manual for Psychopharmacology*. US Department of Health, Education and Welfare; 1976.
20. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep*. 1991;14(6):540-545. doi:10.1093/sleep/14.6.540
21. Postema PG, De Jong JS, Van der Bilt IA, Wilde AA. Accurate electrocardiographic assessment of the QT interval: teach the tangent. *Heart Rhythm*. 2008;5(7):1015-1018. doi:10.1016/j.hrthm.2008.03.037
22. Aman MG, Singh NN, Stewart AW, Field CJ. The aberrant behavior checklist: a behavior rating scale for the assessment of treatment effects. *Am J Ment Defic*. 1985;89(5):485-491.
23. Daniels SR, Greer FR, and the Committee on Nutrition. Lipid screening and cardiovascular health in childhood. *Pediatrics*. 2008;122(1): 198-208. doi:10.1542/peds.2008-1349
24. Holford N, Heo YA, Anderson B. A pharmacokinetic standard for babies and adults. *J Pharm Sci*. 2013;102(9):2941-2952. doi:10.1002/jps.23574
25. Savage VM, Deeds EJ, Fontana W. Sizing up allometric scaling theory. *PLoS Comput Biol*. 2008;4(9):e1000171. doi:10.1371/journal.pcbi.1000171
26. Wang C, Peeters MY, Allegaert K, et al. A bodyweight-dependent allometric exponent for scaling clearance across the human life-span. *Pharm Res*. 2012;29(6):1570-1581. doi:10.1007/s11095-012-0668-x
27. Karlsson MO, Savic RM. Diagnosing model diagnostics. *Clin Pharmacol Ther*. 2007;82(1):17-20. doi:10.1038/sj.clpt.6100241
28. Ette EI. Stability and performance of a population pharmacokinetic model. *J Clin Pharmacol*. 1997;37(6):486-495. doi:10.1002/j.1552-4604.1997.tb04326.x
29. Comets E, Brendel K, Mentré F. Computing normalised prediction distribution errors to evaluate nonlinear mixed-effect models: the npde add-on package for R. *Comput Methods Programs Biomed*. 2008;90(2): 154-166. doi:10.1016/j.cmpb.2007.12.002
30. de Onis M, Onyango AW, Borghi E, Siyam A, Nishida C, Siekmann J. Development of a WHO growth reference for school-aged children and adolescents. *Bull World Health Organ*. 2007;85(9):660-667. doi:10.2471/BLT.07.043497
31. Stevens J, Truesdale KP, McClain JE, Cai J. The definition of weight maintenance. *Int J Obes (Lond)*. 2006;30(3):391-399. doi:10.1038/sj.ijo.0803175
32. Akaike H, Petrov BN, Csaki F. *Second International Symposium on Information Theory*. Akademia Kiado; 1973.
33. Kloosterboer SM, de Winter BCM, Reichart CG, et al. Risperidone plasma concentrations are associated with side effects and effectiveness in children and adolescents with autism spectrum disorder. *Br J Clin Pharmacol*. 2021;87(3):1069-1081. doi:10.1111/bcp.14465
34. Jovanović M, Vučićević K, Miljković B. Understanding variability in the pharmacokinetics of atypical antipsychotics—focus on clozapine, olanzapine and aripiprazole population models. *Drug Metab Rev*. 2020;52(1):1-18. doi:10.1080/03602532.2020.1717517
35. Jeon JY, Chae SW, Kim MG. Population pharmacokinetics of aripiprazole in healthy Korean subjects. *Int J Clin Pharmacol Ther*. 2016; 54(04):293-304. doi:10.5414/CP202466
36. Kim JR, Seo HB, Cho JY, et al. Population pharmacokinetic modelling of aripiprazole and its active metabolite, dehydroaripiprazole, in psychiatric patients. *Br J Clin Pharmacol*. 2008;66(6):802-810. doi:10.1111/j.1365-2125.2008.03223.x
37. Knights J, Rohatagi S. Development and application of an aggregate adherence metric derived from population pharmacokinetics to inform clinical trial enrichment. *J Pharmacokinet Pharmacodyn*. 2015; 42(3):263-273. doi:10.1007/s10928-015-9414-4
38. Koue T, Kubo M, Funaki T, et al. Nonlinear mixed effects model analysis of the pharmacokinetics of aripiprazole in healthy Japanese males. *Biol Pharm Bull*. 2007;30(11):2154-2158. doi:10.1248/bpb.30.2154
39. Aripiprazole Sandoz 10mg tablets—Summary of Product Characteristics (SmPC). 2021. Accessed May 28, 2023. https://www.medicines.org.uk/emc/product/7016/smpc
40. Franken LG, Masman AD, de Winter BCM, et al. Hypoalbuminaemia and decreased midazolam clearance in terminally ill adult patients, an inflammatory effect? *Br J Clin Pharmacol*. 2017;83(8):1701-1712. doi:10.1111/bcp.13259
41. Guo Z, L'Italien GJ, Jing Y, Forbes RA, Hebden T, Kim E. A real-world data analysis of dose effect of second-generation antipsychotic therapy on hemoglobin A1C level. *Prog Neuropsychopharmacol Biol Psychiatry*. 2011;35(5):1326-1332. doi:10.1016/j.pnpbp.2011.03.020
42. Castilla-Puentes R. Effects of psychotropics on glycosylated hemoglobin (HbA1c) in a cohort of bipolar patients. *Bipolar Disord*. 2007;9(7): 772-778. doi:10.1111/j.1399-5618.2007.00534.x
43. Nicol GE, Yingling MD, Flavin KS, et al. Metabolic effects of antipsychotics on adiposity and insulin sensitivity in youths: a randomized clinical trial. *JAMA Psychiatry*. 2018;75(8):788-796. doi:10.1001/jamapsychiatry.2018.1088
44. Grajales D, Ferreira V, Valverde AM. Second-generation antipsychotics and dysregulation of glucose metabolism: beyond weight gain. *Cell*. 2019;8(11):1336. doi:10.3390/cells8111336

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Hermans RA, Sassen SDT, Kloosterboer SM, et al. Towards precision dosing of aripiprazole in children and adolescents with autism spectrum disorder: Linking blood levels to weight gain and effectiveness. *Br J Clin Pharmacol*. 2023;1-11. doi:10.1111/bcp.15800