Expert Opinion on Drug Safety

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ieds20

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To cite this article: Sanne M. Kloosterboer , Denise Vierhout , Jana Stojanova , Karin M. Egberts , Manfred Gerlach , Gwen C. Dieleman , Manon H. J. Hillegers , Kimberly M. Passe , Teun van Gelder , Bram Dierckx & Birgit C. P. Koch (2020): Psychotropic drug concentrations and clinical outcomes in children and adolescents: a systematic review, Expert Opinion on Drug Safety, DOI: 10.1080/14740338.2020.1770224

To link to this article: https://doi.org/10.1080/14740338.2020.1770224

Accepted author version posted online: 18 May 2020.
Published online: 07 Jul 2020.

EXPERT OPINION ON DRUG SAFETY
https://doi.org/10.1080/14740338.2020.1770224

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REVIEW

Psychotropic drug concentrations and clinical outcomes in children and adolescents: a systematic review

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ABSTRACT

Introduction: The use of psychotropic drugs in children and adolescents is widespread but associated with suboptimal treatment effects. Therapeutic drug monitoring (TDM) can improve safety of psychotropic drugs in children and adolescents but is not routinely performed. A major reason is that the relationship between drug concentrations and effects is not well known.

Areas covered: This systematic review evaluated studies assessing the relationship between psychotropic drug concentrations and clinical outcomes in children and adolescents, including antipsychotics, psychostimulants, alpha-agonists, antidepressants, and mood-stabilizers. PRISMA guidelines were used and a quality assessment of the retrieved studies was performed. Sixty-seven eligible studies involving 24 psychotropic drugs were identified from 9,298 records. The findings were generally heterogeneous and the majority of all retrieved studies were not of sufficient quality. For 11 psychotropic drugs, a relationship between drug concentrations and side-effects and/or effectiveness was evidenced in reasonably reported and executed studies, but these findings were barely replicated.

Expert opinion: In order to better support routine TDM in child- and adolescent psychiatry, future work must improve in aspects of study design, execution and reporting to demonstrate drug concentration-effect relationships. The quality criteria proposed in this work can guide future TDM research.

Systematic review protocol and registration
PROSPERO CRD42018084159

ARTICLE HISTORY
Received 15 January 2020
Accepted 13 May 2020

KEYWORDS
Drug monitoring; psychopharmacology; systematic review; child; adolescent; antidepressant; antipsychotic; stimulant; mood stabilizer

1. Introduction

Psychotropic drugs have been proven effective for the treatment of a wide range of psychiatric disorders in children and adolescents. As a result, the use of stimulants, antipsychotics, antidepressants, and mood-stabilizers in youths is widespread [1–3].

However, the use of psychotropic drugs in youth faces several challenges. Some side effects of these drugs appear more prevalent in young patients, like metabolic and endocrine abnormalities associated with antipsychotic drug use [4]. This also applies to selective serotonin reuptake inhibitors (SSRIs), where children seem more vulnerable for restlessness and vomiting [5]. At the same time, efficacy of some psychotropic drugs may be lower in children than in adults, as demonstrated for antidepressants [6].

Although the mechanisms behind suboptimal treatment effects in youths are not fully understood, both *pharmacokinetic* and *pharmacodynamic* changes during childhood might contribute. Pharmacokinetic changes that occur during childhood [7] may result in over- or underdosing in young patients, leading to unanticipated failures of randomized controlled drug trials in child- and adolescent psychiatry [8]. Also pharmacodynamics might influence suboptimal psychotropic treatment effects in children and adolescents, as brain development and target receptor maturation are suggested to be related to the failure of many antidepressants in youths [9]. However, age-specific pharmacokinetic and – dynamic aspects relevant for psychotropic drugs in children and adolescents are largely unknown.

Therapeutic Drug Monitoring (TDM), which comprises the quantification of drug concentrations in blood or other matrices to optimize individual drug dosing [10], incorporates individual pharmacokinetic and pharmacodynamic processes. TDM has proven to enhance efficacy and safety of many psychotropic drugs in adults and has become routine practice for mood stabilizers like lithium, tricyclic antidepressants like amitriptyline, and antipsychotics like clozapine in adult psychiatry [10]. TDM is especially indicated for patient populations with altering pharmacokinetics and pharmacodynamics, such as elderly, pregnant women, children, and adolescents, where both efficacy and side-effects might be unpredictable

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Supplemental data for this article can be accessed here.

Article highlights

- The concentration-effect relationships of psychotropic drugs in children and adolescents are largely unknown, which hampers the routine application of Therapeutic Drug Monitoring (TDM) in this population.
- Our systematic literature search favors a concentration-effect relationship for 11 psychotropic drugs in children and adolescents with different indications, but evidence is sparse and therapeutic reference ranges are generally not evaluated or reported.
- Most retrieved studies did not accurately report or execute key aspects of TDM.
- Even when therapeutic reference ranges are not well established, TDM can improve psychopharmacotherpay when non-compliance, drug–drug interactions, or pharmacogenetic polymorphisms are suspected in children and adolescents.

This box summarizes key points contained in the article.

Table 1. In- and exclusion criteria for selection of relevant articles.

Inclusion criteria	Exclusion criteria
• The study concerns antipsychotics, psychostimulants, antidepressants or mood-stabilizers, alpha-agonists	• No analysis on relationship between drug levels and clinically relevant outcome measures is reported
• Study is performed in children or adolescents aged up to 18 years	• Drug under study is used for non-psychiatric indications (f.e. epilepsy or enuresis)
• Drug plasma levels are measured and reported	• Maternal use during pregnancy or lactation
• Direct clinical outcome measures are reported, i.e. safety or efficacy[a]	• Non-human subjects
	• Studies focusing on toxicology/ overdoses
	• Case reports
	• Conference papers and abstracts
	• Postmortem studies

[a]biomarkers are not regarded a direct clinical outcome measure.

[10,11]. As such, TDM may also provide a measure for proactive pharmacovigilance in children and adolescents [12].

However, TDM within child- and adolescent psychiatry is generally not routinely performed. A major reason is that the relationship between drug concentrations and effects in children and adolescents is not well known, and age- or developmental specific therapeutic reference ranges are lacking [13,14]. The objective of this systematic review is to provide an overview of the literature investigating the relationship between blood concentrations of psychotropic drugs and clinical outcomes in children and adolescents, including stimulants, antipsychotics, antidepressants and mood-stabilizers and alpha-agonists, to further investigate the rationale for TDM in this population. Based on the findings, the current position of TDM within child- and adolescent psychiatry and future research directives are discussed.

2. Methods

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guideline for systematic reviews [15]. This systematic review is registered under PROSPERO number CRD42018084159.

2.1. Information sources

Studies were identified by searching electronic databases and screening reference lists of relevant articles. Three databases were systematically searched without restriction of language or publication date (Embase.com, Medline Ovid and Cochrane CENTRAL). The last search was performed in November 2018. The search strategy can be found in supplementary table 1.

2.2. Eligibility criteria and study selection

Studies reporting the relationship between psychotropic drug concentrations and clinical outcomes (i.e. efficacy or safety) in children or adolescents aged up to 18 years were eligible for inclusion. The included psychotropic drugs were antipsychotics, psychostimulants, alpha-agonists, antidepressants, and mood-stabilizers including anti-epileptics used for psychiatric indications. The eligibility criteria are presented in Table 1.

Title abstract and full-text screen was independently performed by two reviewers (SK and DV); disagreements were resolved by consensus. References of identified studies were checked for relevant articles. Also, previous reviews and the international consensus guideline about TDM in psychiatry were checked for relevant studies [10,13,14].

2.3. Data collection process

One reviewer (SK) extracted the following data from included studies in a data extraction form: (1) characteristics of study participants (including sex, age, and diagnoses), (2) study design (including duration and dosing strategy), (3) outcome measures, (4) blood sample collection (sampling time, relation to steady state) and (5) the results as presented in the study. A second reviewer (KP) checked doubtful items identified by the first reviewer. Disagreements were resolved by discussion between reviewers.

2.4. Quality assessment of therapeutic drug monitoring

To ascertain the internal validity of the selected studies, one reviewer (SK) performed a quality assessment of the therapeutic drug monitoring component of the selected studies. A second reviewer (KP) checked doubtful quality criteria that were identified by the first reviewer during the quality assessment. Disagreements were resolved by discussion between reviewers.

Currently available quality assessment tools do not specifically address drug concentration-effect studies [16], thus criteria for quality assessment were adapted from a previously published meta-analysis of Ulrich et al. concerning the concentration-therapeutic effect relationship of haloperidol in adults [17]. As the current systematic review covers different types of psychotropic drugs with a broad range of indications, not all criteria of the total score as used by Ulrich et al. were applicable. We therefore used only the hard items of the total score. These items are indicated 'sufficient' or 'insufficient' and presented in Table 2. Studies that did not report or did not realize an item were rated insufficient. Premedication was registered as study characteristic and not scored. Furthermore, 'completely insufficient description of study design' was not included as score

Table 2. Criteria for quality assessment of the selected studies.

Quality criteria	Sufficient score	Comments
1. Analytical method for the assay of drug concentration in serum or plasma	– Validated analytical method	
2. Blood sample collection	– Steady state plasma or serum concentrations – Sampling time and drug intake described	
3. Patient selection	– Representative sample for study outcome – Psychiatric classifications and associated classification system are reported	*With a heterogeneous sample, a sub analysis per relevant category should be provided*
4. Measurement of illness severity and registration of therapeutic improvement or worsening	– Adequate quantification of outcome measure (rating with a structured scale) – A baseline assessment of the outcome measure is provided – Adequate calculation of change in outcome measure – Sufficient time to rate effect	*Retrospectively scored change is rated insufficient*
5. Comedication	– No drug that influences pharmacokinetics or pharmacodynamics of the drug under study is taken simultaneously, or: – A sub analysis/correction is provided	
6. Number of patients	– At least 10 patients are included and used for analysis	

item, as individual items were already rated insufficient when the information could not be found.

2.4.1. Analytical method for the assay of drug concentration in serum or plasma

The analytical assay for drug quantification should be selective, able to discriminate the measured drug from other similar drugs and metabolites, and sensitive, accurately quantifying drug concentration [10]. Accurate analytical methods have become available relatively recently [18]. Examples of selective and sensitive methods include chromatographic methods, including High-Performance Liquid Chromatography (HPLC) and Liquid Chromatography-Mass Spectrometry (LC-MS). Older analytical methods like (radio) immunoassay often present high variability in drug quantification. Analytical methods for drug quantification must be validated to demonstrate reliability and reproducibility. The quality assessment of the analytical method was checked per study by a laboratory-based hospital pharmacist (BK).

2.4.2. Blood sample collection

Steady state is achieved when a drug is given in a constant dose and schedule for at least 4–6 half-lives [10]. During steady state, overall bioavailability is in equilibrium with elimination, such that the drug concentration reflects the dosage given. Sampling should therefore be performed during steady state of the drug and its metabolites. An exception is when population pharmacokinetic-pharmacodynamic modeling is performed, which can correct for non-steady state concentrations. Furthermore, the concentration of a drug rises quickly after drug intake and declines afterward as a function of time. An accurate assessment of the time interval between sampling relative to the drug intake is crucial for correct interpretation of the drug concentration. In clinical practice, sampling of the trough concentration is often the standard procedure. The trough concentration is the concentration at the end of a dosing interval, taken immediately before the subsequent dose. The concentration-time curve in the final period of the dose interval is relatively flat, and therefore the exact sampling time is less critical. For normal release methylphenidate formulations, steady state sampling is not relevant due to its short half-life, and thus this item was not weighed in scoring.

2.4.3. Patient selection

A representative sample is important for the generalizability of results (external validity). If a heterogeneous patient group is selected, and there is concern that different relationships exist between drug plasma concentrations and (side-) effects, subgroup analysis should be performed, bearing in mind that adequate power is achieved. Furthermore, psychiatric classifications within the sample and the associated classification system should be reported, as concentration reference ranges are disorder-specific.

2.4.4. Measurement of illness severity and registration of therapeutic improvement or worsening

For the analysis of the relationship between drug concentrations and effect, it is important to assess the effect that is likely to be attributable to the drug. Therefore, a baseline assessment of the severity of the outcome measure, prior to drug treatment, is essential. The change from baseline should be used for analyses rather than a point measurement during treatment. Preferably a validated rating scale should be used to determine outcome measures. Lastly, a sufficient time to rate effect should be considered. For example with antipsychotics, a delay of at least 1 week after start of treatment is expected to observe a clinical effect [17].

2.4.5. Comedication

Comedication can influence the effect of drug trough pharmacokinetic and pharmacodynamic interactions. In particular, pharmacodynamic interactions might confound the observed clinical effects. Co-medication should be taken into account and corrected for when necessary, where possible trough strategies such as stratification or multivariate methods.

2.4.6. Number of patients

Power calculations are challenging in observational studies, and in the setting of observational studies in TDM. Ulrich et al. [17] suggest a minimum of 10 patients, which was rated a sufficient number within our quality assessment.

3. Results

3.1. Study selection

Figure 1 shows the process by which articles were identified. Screening of title and abstract identified 311 primary studies. Full-text was not available for 43 of these.

Sixty-seven studies were included after full-text screen, representing 24 psychotropic drugs: two stimulants, one alpha-agonist, six SSRI's, five tricyclic antidepressants, one other antidepressant, seven antipsychotics, and two mood stabilizers.

Of the selected studies, 35.8% evaluated efficacy measures, 32.8% evaluated side-effect measures and 31.3% evaluated both. A substantial proportion of studies was performed prior to 1995 (n = 23, 34.3%). Most studies were performed in the United States (n = 42, 62.7%), and 25.3% of studies were performed in Europe.

3.2. Quality assessment

Twenty-one studies met all six quality criteria (31.3%), while 47 studies did not meet quality criteria in full (one study described two trials, and fulfilled all criteria for one trial [19]). Five criteria were met in 25 studies (37.3%).

The most frequently missed criterion was *comedication* and *blood sample collection*. Comedication was rated as insufficient in 25 studies (37.3%); it was unreported in 9 studies (13.4%) and was not addressed in analyses in 16 studies (22.4%). Blood sample collection was insufficient in 24 studies (35.8%), where either sampling in steady state was not performed, or time point of sampling relative to the drug intake was not described. *Measurement of illness severity and registration of therapeutic improvement or worsening* was rated as insufficient in 20 studies (29.9%), principally as baseline measurement was not performed. The *analytical method* was scored insufficient in 10 studies (14.9%), the method was judged nonselective or nonsensitive in 3 studies, and the analytical method was not reported in 7 studies.

The characteristics, results, and quality assessment of the studies are presented in Table 3.

The studies meeting all quality criteria involved 15 psychotropic drugs. A concentration–efficacy relationship was found for six drugs (citalopram [51], fluoxetine [51], nortriptyline [52], buproprion [53], quetiapine [54], lithium [55]), a concentration-

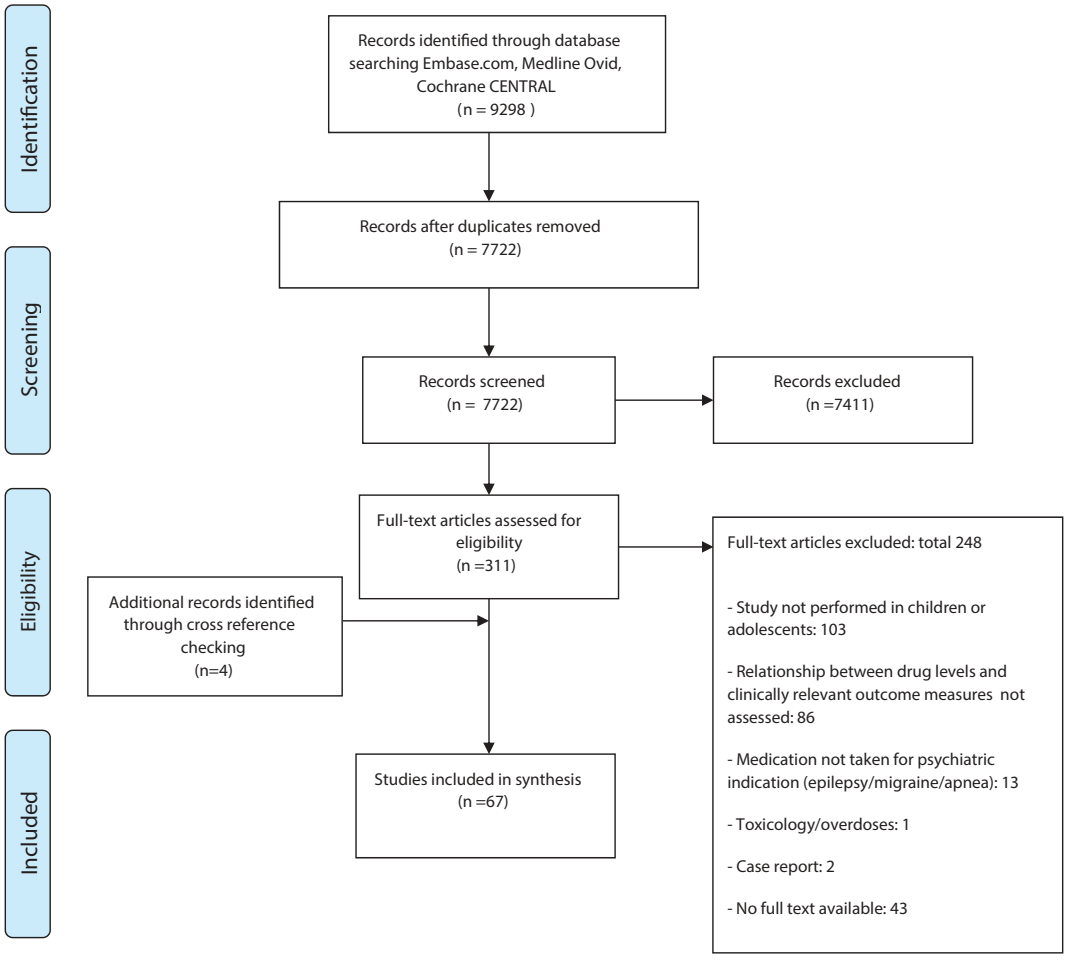

Figure 1. Flowchart.

Table 3. Results.

Study	Drug	No of subjects (males)[a]	Indications	Study design	Concentration-effect relationship: Efficacy	Concentration-effect relationship: Side-effects	No concentration effect-relationship: Efficacy	No concentration effect-relationship: Side-effects	Therapeutic range	Quality assessment: 1	2	3	4	5	6
ADHD drugs															
Hazell et al., 2009 [20]	Atomoxetine	156 (123)	AHDH and ODD	Cohort nested in randomized controlled trial (with non-controlled extension phase)			SNAP-IV ODD and SNAP-IV ADHD, CGI-I			X	X	X	X	X	X
Quinn et al., 2004 [58]	Methylphenidate (NR)	31 (31)	ADHD	Cohort nested in randomized controlled trial (single dose)	Math test					X	X	X	X	X	X
Shaywitz et al., 1982 [19] (acute study)	Methylphenidate (NR)	14 (14)	ADD	Prospective cohort (single dose)		GH, PRL		Glucose		X	X	X	X	X	X
Teicher et al., 2006 [59]	Methylphenidate (NR)	48 (48)	ADHD	Cohorts nested in randomized controlled trial (double-blind, parallel group of five dosing paradigms and placebo)	Computer driven vigilance task (M-MAT)					X	X	X	X	X	X
Teuscher et al., 2018 [60]	Methylphenidate (NR)	81 (53)	ADHD	Pooled analysis of 3 prospective cohort studies (single dose) and 1 cohort nested in randomized controlled trial	SKAMP scale				EC_{50} 14.24 ng/ml	X	X	X	X	X	X
Michelson et al., 2007 [64]	Atomoxetine	338 (?)	ADHD	Pooled analysis of 14 prospective cohort studies and cohorts nested in randomized controlled trials.	ADHD Rating Scale-IV-Parent					X			X		X
Brown et al., 1979 [21]	Dexamphetamine	16 (16)	Hyperactivity	Cohort nested in randomized controlled trial (single dose)				Behavioral and and motor activity			X	X	X		X
Greenhill et al., 2001 [78]	Methylphenidate	8 (8)	ADHD	Prospective cohort	Motor performance errors		Self-rating form		EC_{50} 10 ng/ml	X		X	X		
Gualtieri et al., 1981 [22]	Methylphenidate (NR)	27 (?)	Hyperactivity	Cohort nested in randomized controlled trial (single dose)		GH		PRL		X	X				X

(*Continued*)

Table 3. (Continued).

					Concentration-effect relationship		No concentration effect-relationship			Quality assessment					
Study	Drug	No of subjects (males)[a]	Indications	Study design	Efficacy	Side-effects	Efficacy	Side-effects	Therapeutic range	1	2	3	4	5	6
Gualtieri et al., 1984 [85] study I	Methylphenidate (NR)	55 (39)	ADHD	Cohort nested in randomized controlled trial			Global response rating scale, CTRS, laboratory measures of attention and activity, behavioral observations	SERS, pulse, BP, GH, PRL		X	X	X		X	X
Gualtieri et al., 1984 [85] study II	Methylphenidate (NR)	26 (22)	ADHD	Prospective cohort (single dose)			CTRS			X	X	X		X	X
Gualtieri et al., 1984 [85] study III	Methylphenidate (NR)	11 (?)	ADHD	Prospective cohort (single dose)				GH, PRL		X	X			X	X
Gualtieri et al., 1984 [85] study VI	Methylphenidate (NR)	4 (?)	ADHD	Prospective cohort			Performance task, behavior observations, CTRS			X				X	X
Jonkman et al., 1998 [23]	Methylphenidate (NR)	12 (11)	ADHD	Prospective cohort (single dose)	Event-related brain potentials					X	X	X	X		X
Kimko et al., 2012 [24]	Methylphenidate (ER)	Unknown	ADHD	Meta-analysis	SKAMP scale, PERMP				EC_{50} 7.55/7.69 ng/ml		X		X		X
Sebrechts et al., 1986 [25]	Methylphenidate (NR)	12 (12)	ADHD	Cohort nested in randomized controlled trial	MFFT test					X	X	X	X		X
Shaywitz et al., 1982 [19] (chronic study)	Methylphenidate (NR)	11 (?)	ADD	Prospective cohort (single dose)	CAPTRS					X	X	X	X		X
Srinivas et al., 1992 [26]	Methylphenidate (NR)	9 (9)	ADHD	Cohort nested in randomized controlled trial			SRT scores (d-enantiomer)			X	X		X	X	
Winsberg et al., 1982 [27]	Methylphenidate (NR)	25 (25)	ADHD	Cohort nested in randomized controlled trial	CTRS, WWPAS		Short term memory tasks				X	X			X
Selective Serotonin Reuptake Inhibitors															
Sakolsky et al., 2011 [51]	Citalopram	27 (?), n with plasma samples 244 (?)	MDD	Cohort nested in randomized non-controlled trial	CDRS-R, CGI-I			SEFCA		X	X	X	X	X	X
Sakolsky et al., 2011 [51]	Fluoxetine	64 (?), n with plasma samples 244 (?)	MDD	Cohort nested in randomized non-controlled trial	CDRS-R, CGI-I			SEFCA		X	X	X	X	X	X
Sakolsky et al., 2011 [51]	Venlafaxine	119 (?),n with plasma samples 244 (?)	MDD	Cohort nested in randomized non-controlled trial		Dizziness,	cardiovascular and dermatologic adverse events (SEFCA)	CDRS-R, CGI-I			X	X	X	X	X

X

(*Continued*)

Table 3. (Continued).

Study	Drug	No of subjects (males)[a]	Indications	Study design	Concentration-effect relationship: Efficacy	Concentration-effect relationship: Side-effects	No concentration effect-relationship: Efficacy	No concentration effect-relationship: Side-effects	Therapeutic range	Quality assessment: 1	2	3	4	5	6
Sakolsky et al., 2011 [51]	Paroxetine	34 (?), n with plasma samples 244 (?)	MDD	Cohort nested in randomized non-controlled trial			CDRS-R, CGI-I	SEFCA		X	X	X	X	X	X
Blázquez et al., 2014) [28]	Fluoxetine	73 (24)	MDD, OCD, generalized anxiety disorder	Prospective cohort	CY-BOCS (OCD patients, n = 12)		CGI-I (total sample)	UKU SERS (total sample)		X		X	X		X
Koelch et al., 2012 [29]	Fluoxetine	71 (27)	Depressive disorder or depressive symptoms	Retrospective cohort			CGI-I	UKU SERS		X		X			X
Reinblatt et al., 2009 [65]	Fluvoxamine	fluvoxamine: 22 (12), placebo: 23 (12)	Anxiety disorders	Prospective cohort		Activation cluster adverse events				X		X	X	X	X
Alderman et al., 1998 [30]	Sertraline	61 (33)	OCD, MDD or both	Prospective cohort				Adverse events (reported by the patient of observed by the investigator)		X	X	X		X	X
Alderman et al., 2006 [31]	Sertraline	43 (18)	OCD or MDD	Prospective cohort			CGI-I, CGI-S			X		X	X	X	X
Taurines et al., 2013 [66]	Sertraline	90 (41)	Children and adolescents receiving sertraline	Retrospective cohort		UKU SERS (patients with depression)	CGI-I	UKU SERS		X		X		X	X
Tricyclic Antidepressants															
Moen Olig et al., 1985 [32]	Amitriptyline	10 (?)	MDD	Prospective cohort			Telephone monitoring of clinical response, CDI			X	X	X	X	X	X
Flament et al., 1985 [33]	Clomipramine	19 (14)	OCD	Cohort nested in randomized controlled trial			LOI-CV, OCR scale, CPRS, NIMH Global Scale, BPRS, NIMH self- rating scale			X	X	X	X	X	X
Biederman et al., 1989 [34]	Desipramine	56 (?)	ADHD	Randomized controlled trial followed by prospective cohort (placebo non-responders)			CGI	ECG parameters		X	X	X	X	X	X
Donnelly et al., 1986 [56]	Desipramine	29 (29), 15 receiving desipramine	ADHD	Cohort nested in randomized controlled trial		HR (day 14)	CABRS (teacher ratings)	BP		X	X	X	X	X	X

(*Continued*)

Table 3. (Continued).

Study	Drug	No of subjects (males)[a]	Indications	Study design	Concentration-effect relationship: Efficacy	Concentration-effect relationship: Side-effects	No concentration effect-relationship: Efficacy	No concentration effect-relationship: Side-effects	Therapeutic range	Quality assessment 1	2	3	4	5	6
Spencer et al., 2002 [35]	Desipramine	41 (34)	combined-type ADHD and chronic motor tic disorder, chronic vocal tic disorder, or Tourette disorder (TD)	Cohort nested in randomized controlled trial			CGI and specific rating scale (ADHD Rating Scale, YGTSS, CY-BOCS, CDI, RCMAS, and GAF)	Adverse events by open ended questions, ECG		X	X	X	X	X	X
Preskorn et al., 1983 [61]	Imipramine	22 (17)	MDD	Prospective cohort		Diastolic BP, HR and slowing of intracardiac conduction		Subjective reports of side-effects	<225 ng/ml	X	X	X	X	X	X
Puig-Antich et al., 1979 [62]	Imipramine	13 (9)	MDD	Prospective cohort	K-SADS				> 146 ng/ml.	X	X	X	X	X	X
Puig-Antich et al., 1987 [63]	Imipramine	30 (18)	MDD	Prospective cohort	K-SADS-P					X	X	X	X	X	X
Moen Olig et al., 1985 [32]	Imipramine	10 (?)	MDD	Prospective cohort			Telephone monitoring of clinical response, CDI			X	X	X	X	X	X
Geller et al., 1985 [36]	Nortriptyline	21 (14)	MDD	Prospective cohort				ECG measurements		X	X	X	X	X	X
Geller et al., 1986 [52]	Nortriptyline	22 (16)	MDD	Prospective cohort	Children depression rating scale			-	>60 ng/ml	X	X	X	X	X	X
Birmaher et al., 1998 [37]	Amitriptyline	27 (8)	MDD	Cohort nested in randomized controlled trial			K-SADS-P, HDRS, CGI, BDI, C-GAS	Side effects scale, ECG, vital signs				X	X	X	X
Dugas et al., 1980 [67]	Clomipramine	10 enuretic children (10), 26 depressive children (9)	Children with depressive		symptomatology or enuresis	Prospective cohort		Hospital side-effects checklist	Clinical status			X	X		
	X														
Biederman et al., 1993 [38]	Desipramine	71 (?)	ADHD or depression	Cross-sectional		ECG: paired premature atrial contractions		24 h Holter, ECG, Doppler echo-cardiography, cardiac exam			X	X			X
Wilens et al., 1993a [39]	Desipramine	89 (79)	Various diagnoses (MDD and ADHD)	Prospective cohort				ECG-changes, HR		X		X	X	X	X
Ryan et al., 1986 [40]	Imipramine	34 (17)	MDD	Prospective cohort			K-SADS-P			X		X	X	X	X
Ambrosini et al., 1994 [82]	Nortriptyline	25 (14)	MDD	Prospective cohort			M-SADS, BDI		Greater response for 50–150 ng/ml (adult range)			X	X		X
Wilens et al., 1993b [83]	Nortriptyline	82 (68)	Children treated with nortriptyline	Retrospective cohort		Interventricular Conduction Delay (IVCD)		Abnormal ECG	> 150 ng/ml (IVCD)	X	X	X	X		X
Other antidepressants															

(*Continued*)

Table 3. (Continued).

Study	Drug	No of subjects (males)[a]	Indications	Study design	Concentration-effect relationship: Efficacy	Concentration-effect relationship: Side-effects	No concentration effect-relationship: Efficacy	No concentration effect-relationship: Side-effects	Therapeutic range	Quality assessment: 1	2	3	4	5	6
Burleson Daviss et al., 2006 [53]	Bupropion	16 (8)	MDD or depressive disorder not otherwise specified	Prospective cohort	CGI-I				7.5 hours after morning dose: >37 ng/ml (provide cutoff for metabolites)	X	X	X	X	X	X
Antipsychotics															
Findling et al., 2006 [54]	Quetiapine	17 (16), analyzed n = 10 at week 8	Conduct disorder and comorbid ADHD	Prospective cohort	CGI-I (week 8)				1-hour post-dose >300 ng/mL	X	X	X	X	X	X
Sallee et al., 2003 [57]	Ziprasidone	24 (19)	Tourette syndrome or chronic tic disorder	Prospective cohort (single dose)		PRL				X	X	X	X	X	X
Sallee et al., 2006 [41]	Ziprasidone	24 (19)	Tourette or chronic tics	Prospective cohort (single dose)				QTc interval		X	X	X	X	X	X
Alfaro et al., 2002 [69]	Clozapine	24 (19)	Schizophrenia or psychotic disorder not otherwise specified	Randomized controlled trials and prospective cohorts				PRL		X		X	X		X
Frazier et al., 2003 [76]	Clozapine	24 (19)	Childhood onset schizophrenia	Prospective cohort and randomized controlled trial	SANS	Subjective Treatment Emergent Symptoms Scale				X	X	X	X	X	
Sporn et al., 2007 [75]	Clozapine	6 weeks follow-up: 54 (34), long term follow-up: 33 (22)	Schizophrenia	Cohorts nested in randomized controlled trials and prospective cohort studies	desmethylclozapine/clozapine ratio: BPRS, SAPS (week 6)		Desmethylclozapine/clozapine ratio: SANS (week 6), CGAS (2–6 years).		desmethylclozapine and clozapine concentrations: BPRS, SAPS, SANS, CGAS						
Side effects recorded by treating physician (6 weeks)				X	X		X								
Wohkittel et al., 2016 [77]	Clozapine	68 (33)	Various diagnoses, 70% childhood schizophrenia	Retrospective cohort		UKU SERS	CGI-S and CGI-I		< 317 ng/ml	X	X	X			X
Alfaro et al., 2002 [69]	Haloperidol	15 (9)	Schizophrenia or psychotic disorder not otherwise specified	Cohorts nested in randomized controlled trials and prospective cohorts				PRL		X		X	X		X
Morselli et al., 1979 [68]	Haloperidol	23 (14)	Psychotic disorder not otherwise specified	Prospective cohort		Side effects (unspecified)			< 6 ng/ml. For Gilles de la Tourette positive response in range 1–4 ng/ml (n = 5)	X	X				X

(*Continued*)

Table 3. (Continued).

Study	Drug	No of subjects (males)[a]	Indications	Study design	Concentration-effect relationship		No concentration effect-relationship		Therapeutic range	Quality assessment					
					Efficacy	Side-effects	Efficacy	Side-effects		1	2	3	4	5	6
Slooff et al., 2018 [42]	Haloperidol	13 (5)	Pediatric delirium	Prospective cohort				Adverse events by predefined list and Naranjo score		X		X	X	X	X
Selim et al. [43]	Loxapine	30 (13)	Non-agitated children and adolescents with chronic antipsychotic use	Single fixed dose	Pharmacokinetic study (inhalation)				Sedation		X	X	X	X	
X															
Alfaro et al., 2002 [69]	Olanzapine	12 (7)	Schizophrenia or psychotic disorder not otherwise specified	Cohorts nested in randomized controlled trials and prospective cohorts		PRL				X		X	X		X
Fekete et al., 2017 [79]	Olanzapine	115 (47)	Various diagnoses	Retrospective cohort			CGI-I and CGI-S	UKU SERS	20–80 ng/ml	X	X	X			X
Migliardi et al., 2009 [70]	Olanzapine	13 (7)	Various diagnoses	Prospective cohort		PRL (in females)				X		X	X	X	X
Albantakis et al., 2017 [44]	Quetiapine	180 (82)	Various diagnoses	Retrospective cohort		UKU SERS	CGI-I and CGI-S		<100 ng/ml	X	X	X		X	X
Gerlach et al., 2007 [88]	Quetiapine	21 (12)	Schizophrenia and schizoaffective psychosis	Prospective cohort			BPRS	DOTES, weight, ECG		X	X	X			X
Dos Santos-Junior et al., 2017 [89]	Risperidone	67 (51)	Various diagnoses	Cross-sectional				BMI z-scores; BP z-scores; serum glucose and insulin, TC and fractions; TG; LFTs; leptin		X	X	X		X	X
Duval et al., 2008 [71]	Risperidone	16 (10)	Schizophreniform disorder	Prospective cohort		PRL				X	X	X		X	X
Gagliano et al., 2004 [45]	Risperidone	20 (14)	Autistic disorder. Mental retardation was present in all subjects	Prospective cohort			CPRS-14	PRL		X		X	X	X	X
Klampfl et al., 2010 [80]	Risperidone	103 (85)	Impulsive aggressive symptoms, (74% of subjects disruptive behavior disorder)	Retrospective cohort			CGI	UKU SERS	8–26 ng/ml	X	X	X		X	X
Migliardi et al., 2009 [70]	Risperidone	29 (22)	Various diagnoses	Prospective cohort		PRL (in males)				X		X	X	X	X

(*Continued*)

Table 3. (Continued).

Study	Drug	No of subjects (males)[a]	Indications	Study design	Concentration-effect relationship: Efficacy	Concentration-effect relationship: Side-effects	No concentration effect-relationship: Efficacy	No concentration effect-relationship: Side-effects	Therapeutic range	Quality assessment: 1	2	3	4	5	6
Ngamsamut et al., 2016 [72]	Risperidone	103 (90)	Autism spectrum disorder according to DSM	Cross-sectional		PRL				X	X	X		X	X
Roke et al., 2012 [73]	Risperidone	51 (51) and comparison group of 47 (47)	Autism spectrum disorder or disruptive behavior disorder	Cross-sectional		PRL						X			X
Troost et al., 2007 [74]	Risperidone	25 (23)	Pervasive developmental disorder according to DSM IV	Prospective cohort		PRL				X		X		X	X
Correll et al., 2011 [46]	Ziprasidone	29 (13)	Various diagnoses	Prospective cohort				QTc duration and dispersion		X		X	X	X	X
Mood stabilizers															
Landersdorfer et al., 2017 [55]	Lithium	61 (32)	Bipolar-I disorder	Prospective cohort	YMRS				EC_{50} 0.711 mEq/L	X	X	X	X	X	X
Amitai et al., 2014 [47]	Lithium	61 (31)	Bipolar and non-bipolar disorder	Retrospective cohort				WBCs, sCR or TSH blood levels		X		X	X	X	X
Patel et al., 2006 [48]	Lithium	27 (22)	Depression associated with Bipolar I disorder	Prospective cohort	CGI-BP		CDRS-R			X		X	X		X
Siegel et al., 2014 [49]	Lithium	30 (23)	Autism Spectrum Disorder	Retrospective cohort			CGI-I					X			X
Amitai et al., 2015 [50]	Valproic acid	104 (68)	Children treated with VPA at a psychiatric ward	Retrospective cohort				WBCs, PLT counts, TSH, LFTs, amylase levels or metabolic parameters					X	X	X

Legend:

[a]Number of subjects with analysis on drug concentrations and effect.

Each drug assessed within a study represents a row in the table; one study can therefore be in the table more than once. If an item was not described in the study, the item was not scored. Only outcomes that were analyzed are mentioned. Relationships may concern the mother compound, metabolite, or both.

ADD = Attention Deficit Disorder; ADHD = Attention Deficit Hyperactivity Disorder; BMI = body mass index; BP = blood pressure; BPRS = Brief Psychiatric Rating Scale; CABRS = Conners Abbreviated Rating Scale; CAPTRS = Conner's Abbreviated Parent Teacher Rating Scale; CDI = Children's Depression Inventory; CDRS-R = Children's Depression Rating Scale – revised; C-GAS = Childrens Global Assessment Scale; CGI-I = Clinical Global Impression improvement Scale; CGI-S = Clinical Global Impression severity Scale; CPRS = comprehensive Psychopathological Rating Scale; CTRS = Conner's Teaching Rating Scale; CY-BOCS = Childrens' Yale-Brown Obsessive Compulsive Scale; CY-BOCS = The Children's Yale-Brown Obsessive Compulsive Scale; DOTES = Dose Record and Treatment Emergent Symptom Scale; EC_{50} = half maximal effective concentration, the concentration of a drug which induces a response halfway between the baseline and maximum; ECG = electrocardiogram; ER = extended release formulation; GAF = Global Assessment of Functioning; GH = growth hormone; HDRS = Hamilton Depression Rating Scale; HR = heart rate; K-SADS = Kiddie Schedule for Affective Disorders and Schizophrenia; K-SADS-P = Schedule for Affective Disorders and Schizophrenia for School Age Children (6–18) Present Episode; LFTs = liver function tests; LOI-CV = Leyton Obsessional Inventory-Child version; MDD = Majpr Depressive Disorder; MFFT = Matching Familiar Figures Test; M-MAT = McLean Motion Attention Test; M-SADS = abbreviated Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS), just covering affective symptoms; NIMH = National Institute of Mental Health; NR = normal release; OCD = obsessive-compulsive disorder; OCR Scale = Obsessive-Compulsive Rating Scale; ODD = Oppositional defiant disorder; PERMP = Permanent Product Measure of Performance; PLT = platelet, PRL = prolactin; RCMAS = Revised Children's Manifest Anxiety Scale; sCR = serum creatinine; SEFCA = Side Effects Form for Children and Adolescents; SERS = Side Effects Rating Scale; SKAMP = Swanson, Kotkin, Agler, M-Flynn and Pelham Scale; SNAP = Swanson, Nolan, and Pelham Questionnaire; SRT = Scanning Reaction Time, part of three computer tests; TC = total cholesterol; TG = triglycerides; TSH = thyroid stimulating hormone; UKU = Udvalg for Klinske Undersogelser; WBC: white blood cell counts; WWPAS = Werry-Weiss Peters Activity Scale; YGTSS = Yale Global Tic Severity Scale.

side-effects relationship was found for three (venlafaxine [51], desipramine [56], ziprasidone [57]), and a relationship with both efficacy and side-effects for two (methylphenidate [19,58–60], imipramine [61–63]). The indications for use of these drugs included major depression, conduct disorder, bipolar disorder, attention-deficit disorder with or without hyperactivity and Tourette syndrome or chronic tic disorder (Table 3). In seven of the studies meeting all quality criteria, therapeutic reference ranges or concentrations for optimal treatment were reported [52–55,60–62].

The 47 studies that did not meet all quality criteria involved 20 psychotropic drugs, for which concentration-effect relationships were reported for 13. These concerned eight additional drugs compared to the studies judged high-quality studies: one with a concentration–efficacy relationship (atomoxetine [64]), six with a concentration-side-effect relationship (fluvoxamine [65], sertraline [66], clomipramine [67], haloperidol [68], olanzapine [69,70], risperidone [70–74]), and one with both (clozapine [75–77]). In nine of the studies with lower quality, suggested therapeutic reference ranges or optimal concentrations were reported [67,68,77–83].

For 5 of the 24 psychotropic drugs that were retrieved with our search, no relationship between concentration and clinical outcomes was found in either high-quality studies or lower-quality studies (dexamphetamine, paroxetine, imipramine, loxapine, valproic acid).

Overall, findings were highly heterogeneous. Most studies were not primarily designed to assess the relationship between drug concentrations and effects. Furthermore, most of the studies were not replicated and for most drugs and outcomes, only one study was available.

4. Conclusions

This systematic review presents published evidence for the relationship between drug concentration and clinical outcomes of psychotropic drugs in children and adolescents. We found a minority of therapeutic drug monitoring studies were reasonably reported and executed. Among these, concentration-effect relationships were evidenced for methylphenidate, citalopram, fluoxetine, venlafaxine, desipramine, imipramine, nortriptyline, bupropion, quetiapine, ziprasidone, and lithium, for various indications in children and adolescents. However, findings were often heterogeneous, barely replicated and therapeutic reference ranges were not often provided. Moreover, interpretation of data from retrieved studies was primarily complicated by inappropriately conducted or inadequately reported sampling.

5. Expert opinion

5.1. Considering the relevance of a drug concentration-effect relationship in the clinical context

Although for a wide range of psychotropic drugs some evidence was found for a concentration-effect relationship, its relevance in clinical practice depends on several drug-related and clinical factors [84], including the time-course of the observed effects.

For instance, the relationship between systemic methylphenidate concentrations and efficacy in children and adolescents with Attention-Deficit Hyperactivity Disorder was frequently reported, but might be of questionable relevance. Among 160 children and adolescents across three reasonably reported and executed trials, a higher methylphenidate concentration was associated with improved performance, though different instruments were used across the studies [58–60]. Most studies judged of lower quality reported similar findings, with one exception [85]; however, the length of the follow-up period was unclear in this work, thus the relationship might have been underestimated. These findings suggest that this stimulant might be a candidate for TDM in children and adolescents, although routine application should be carefully considered [84]. As improvement in attention is readily assessable by parents and teachers [86], it is questionable that concentration measurement would further inform clinical decision-making.

TDM may be more informative for psychotropic drugs with delayed therapeutic or side-effects, such as antidepressants or antipsychotic drugs. TDM would ideally provide important information on adequacy of therapy in an early phase, thereby preventing sub-therapeutic treatment and long-term side-effects. Given growing concerns about antipsychotic-induced metabolic abnormalities in children and adolescents [87], these drugs could be an important target for TDM. Unfortunately, no relationship was found in two studies evaluating the relationship between antipsychotic concentrations and metabolic outcomes such as weight, glucose, and fatty acids in children and adolescents [88,89]. However, these studies did not perform baseline measurements and the relationship may be underestimated. Others report associations between higher dose and weight gain [90,91], thus a relationship with systemic concentrations is suspected. Another aspect that should be considered when assessing the relevance of a drug concentration-effect relationship, is the margin between effective and toxic drug concentrations. If this margin is very narrow, as for example for lithium, it is important to closely monitor drug concentrations to prevent intoxications. For this reason, routine TDM is recommended for lithium in children and adolescents [92]. At the same time, for drugs with a very wide window, as generally applies to SSRIs, TDM is expected to be less useful in routine care, but may be useful to objectify nonadherence. Furthermore, the drug concentrations after a given dosage should be difficult to predict. This is referred to as a high *inter-individual* pharmacokinetic variation and means that drug concentrations differ largely between patients after administration of equal dosages. Another aspect that should be considered for the clinical application of TDM, is that a rapid and reliable method for analysis of the drug should be available. Lastly, before TDM is routinely applied, it should be demonstrated that TDM improves patient outcomes and is cost-effective in clinical practice.

5.2. Research recommendations to support TDM in child- and adolescent psychiatry

A proven drug concentration-effect relationship is the first step to provide a rationale for TDM, but this was only sparsely evidenced for most psychotropic drugs in children and adolescents. In order to better demonstrate drug concentration-effect relationships in this field, future work must improve in aspects of study design, execution, and reporting. Many studies failed to perform standardized sampling, including sampling with respect to steady state and administration time. Therefore, there is a need for an accepted tool for the appraisal of drug concentration-effect studies [10,16]. The assessment criteria proposed by this report could serve as a starting point, hopefully reducing the heterogeneity observed to date, and permitting meta-analyses.

Besides the need for more adequate sampling protocols, also study designs should be considered for their feasibility and appropriateness to demonstrate a drug concentration-effect relationship. Pharmacokinetic and – dynamic research in children with psychiatric morbidities is challenging and is liable to ethical constraints. As such, observational study designs may provide initial estimates toward defining reference ranges for this patient group. However, results should be interpreted in the light of their limitations. Flexible dosing schemes might lead to an underestimation of the concentration-effect relationship due to the placebo effect that is common for psychotropic drugs. Lower dosages, and thus lower drug concentrations, are likely used in placebo-responders, weakening association estimates [93]. Furthermore, observational studies often permit dosage changes and comedication, thereby altering concentrations of the index drug and complicating analyses with respect to outcomes. In particular within child- and adolescent psychiatry, psychotropic comedication is very common and should be considered [94]. Also, non-pharmacological interventions such as behavioral interventions are commonly part of multimodal treatment, possibly influencing therapeutic outcomes. Results of observational work can nevertheless be very valuable, especially when aspects of therapeutic drug monitoring are well-reported and well executed. It may be argued that if dose-effect relationships are apparent in the setting of observational study designs, the effect would be more pronounced in a randomized controlled trial that involves titration to concentrations associated with efficacy.

However, before TDM is routinely applied in clinical practice, preferably its effect on patient outcomes is evaluated. Ideally, to demonstrate that TDM can improve clinical outcomes, randomized controlled trials would be used to evaluate TDM as an intervention, comparing clinician directed dosing with dose adjustment based on drug monitoring, or comparing different target concentrations [10]. Relevant outcomes would include response, side-effects and cost-effectiveness. An excellent example of such a trial investigating effects and side-effects is the randomization to one of the three target concentrations for clozapine in adults [95]; however, no such RCTs have been performed for psychotropic drugs in children and adolescents. This is partly due to difficulties in performing such trials within child- and adolescent psychiatry [96]. However, in general, such RCTs are very rare in the field of TDM and are therefore not always required before its implementation in clinical practice.

5.3. TDM in adult psychiatry

Within adult psychiatry, TDM is generally recommended for lithium, most tricyclic antidepressants, and clozapine. For lithium, TDM is even considered mandatory given its small therapeutic window and relatively high risk for altering concentrations, due to the fully renal excretion and several known drug–drug interactions. The Consensus Guidelines for Therapeutic Drug Monitoring in Neuropsychopharmacology also highly recommends TDM for several other psychotropic drugs in adults, including olanzapine, haloperidol, carbamazepine, and valproate. This guideline provides therapeutic reference ranges in adults, although these ranges are regularly based on observed values in the population rather than based on RCTs. The cost-effectiveness of TDM in adult psychiatry has only poorly been investigated, and RCTs investigating TDM as an intervention have rarely been done. Nevertheless, TDM is, based on considerably better documented concentration-effect relationships than in children and adolescents, considered a helpful and well-accepted tool to improve pharmacopsychiatry in adults.

5.4. Current position of TDM within child- and adolescent psychiatry

Almost no studies reported therapeutic reference ranges for psychotropic drugs in children and adolescents. Unfortunately, ranges cannot be simply extrapolated from adults, as both pharmacokinetic and pharmacodynamic processes differ considerably. This is the result of developmental changes in body composition, target receptor maturation, and organ ripening [7], generally leading to lower psychotropic drug concentrations in children and adolescents than recommended therapeutic reference ranges in adults [12]. Also, psychotropic drugs may be used for other indications in children and adolescents than in adults, and in other dosages, such as antipsychotic drugs (behavioral problems versus psychosis).

The absence of established reference ranges prevents routine application of TDM on a population level. An exception applies to lithium, for which routine TDM is recommended based on a known narrow therapeutic range in adults, which is also applied in children and adolescents [92]. Within our systematic review, one well documented and executed study found a drug concentration-effect relationship in pediatric patients with bipolar I disorder [55], but studies that systematically investigate the added value and optimal concentrations of lithium in clinical practice are lacking. For other psychotropic drugs, despite the unavailability of clear-cut concentration effect-relationships, TDM can be of added value on an individual level when noncompliance is suspected or, drug–drug interactions or pharmacogenetic polymorphisms, for example, in cytochrome 2D6, are foreseen in children and adolescents using psychotropic drugs. A drug concentration measurement can identify unexpected concentrations, as for many antipsychotic drugs expected concentrations based on a given dosage in steady state are known [97]. These are called *pharmacokinetic reference ranges* and can optimize

antipsychotic pharmacotherapy by guiding dose- or comedication adjustments. In this way, TDM can prevent over- or underdosing, and improve psychotropic pharmacological treatment in children and adolescents. As long-term safety data of psychotropic drugs in this population are generally lacking and these drugs are frequently prescribed off-label, TDM can provide an important tool to improve psychopharmacotherapy in children and adolescents.

6. Limitations

The results of this systematic review should be interpreted in the light of its limitations. Firstly, among quality assessment criteria, unreported elements were judged insufficient. However, older work might have reported data on methodological aspects more concisely, thus might have been assessed too strictly. As such, five studies were rated insufficient for the item *comedication*. Secondly, a substantial number of articles were not available full text, primarily reflecting older work. However, based on title and abstract screen, these are not expected to have influenced our conclusions. Thirdly, the older publications also concerned drugs that are currently not widely used in children and adolescents anymore, such as tricyclic antidepressants. Fourthly, publication bias is a possibility that due to heterogeneity we were unable to evaluate, and this may have bias our findings toward positive results. Lastly, the scope of the current review was very broad and aimed at providing an overview of the current literature, which limits a more profound discussion of the individual drugs.

Acknowledgments

The authors acknowledge the contribution of W Bramer and S Gunput of Erasmus MC in performing the search strategy.

Author contributions

All authors are accountable for all aspects of the work and approved the final version to be published. Conception and design: SMK, KME, MG, BD and BCPK. Analysis and interpretation of the data: SMK, DV, JS and KMP. Drafting of the paper: SMK. Revising the paper critically for intellectual content: JS, KME, MG, GCD, MHJH, TvG, BD and BCPK.

Funding

SM Kloosterboer, B Dierckx and BC Koch received grant research support from The Netherlands Organization for Health Research and Development (ZonMW), number [836041011]. KM Egberts received grant research support from the Federal Institute for Drugs and Medical Devices, Bonn [BfArM- reference number: V-15322/68605/2013-2018]. MHJ Hillegers received grant research support from The Netherlands Organization for Health Research and Development (ZonMW), grant 60-63600-98-021.

Declaration of interest

T van Gelder has received lecture fees and study grants from Chiesi and Astellas, in addition to consulting fees from Roche Diagnostics, Vitaeris, Astellas, Aurinia Pharma, and Novartis. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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• ***Provides pharmacokinetic reference values of psychotropic drugs in children and adolescents.***