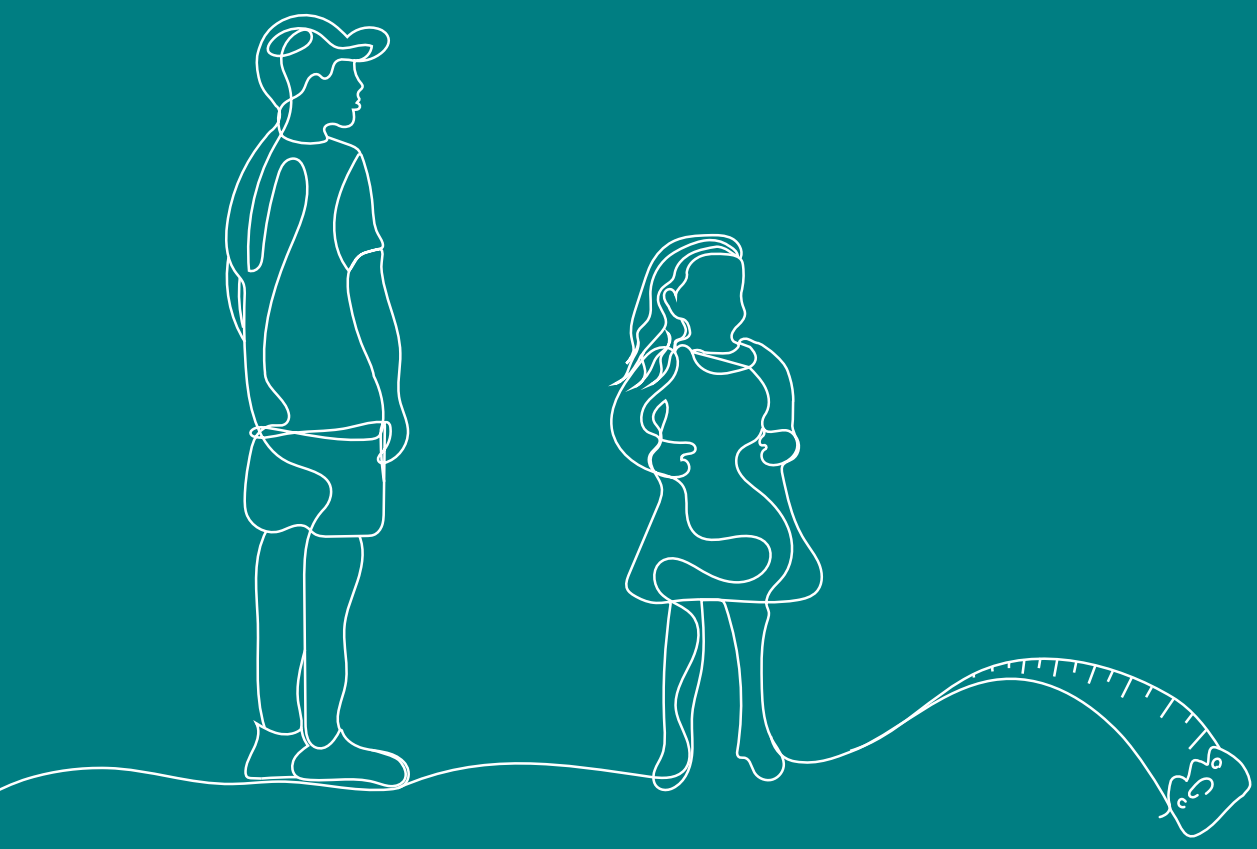
MONITORING FOR ADVERSE DRUG REACTIONS IN CHILDREN AND ADOLESCENTS TREATED WITH ANTIPSYCHOTIC DRUGS

Lenneke Minjon



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Colophon

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Monitoring for adverse drug reactions in children and adolescents treated with antipsychotic drugs

Monitoren van bijwerkingen bij kinderen en adolescenten die behandeld worden met antipsychotica
(met een samenvatting in het Nederlands)

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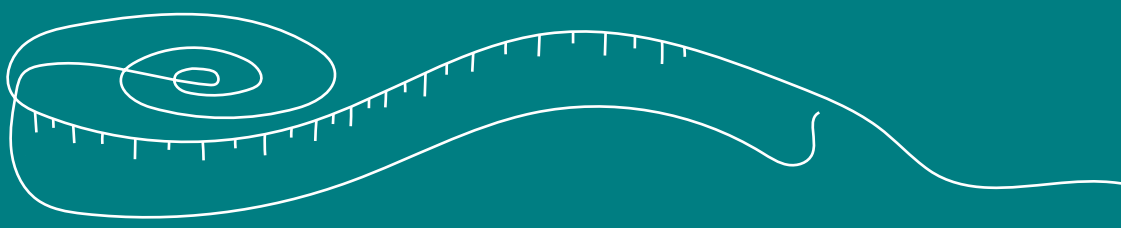
TABLE OF CONTENTS



Chapter 1

General introduction

A boy aged 8 years has been diagnosed with autism spectrum disorder two years ago. Recently, he has developed severe aggressive behavior, which does not affect only himself but also his parents, sister, friends, classmates, and teacher. The child and adolescent psychiatrist offered psychosocial guidance to the parents and teacher, but this was not sufficient. Since the situation threatens to escalate, the child and adolescent psychiatrist suggests starting the child on risperidone, an antipsychotic drug. She is aware of the potential adverse drug reactions, including cardiometabolic disturbances and hyperprolactinemia. As the boy is already somewhat overweight, she wants to carefully monitor whether he will gain more weight. In addition, she wants to draw blood to monitor the glucose, cholesterol, and prolactin blood levels at the start of and during the antipsychotic drug treatment. However, the boy has a fear of needles. She wants to safely prescribe this drug for this boy, but she also does not want the monitoring to be a burden to the child. Therefore, she is not sure of the most optimal way of monitoring him. She searched for clinical guidelines, but the guidelines differ in advice and instructions on how to monitor children treated with an antipsychotic drug and these are not completely clear. Although the boy and his parents are relieved that there may be a drug that can help, they also have several questions, including "Do you have to take the drug every day?" and "Does it cause many adverse drug reactions?" The child and adolescent psychiatrist wants to study recent insights in the clinical practice guidelines and discuss the pharmacotherapy with the pharmacist to provide the most optimal and tailored antipsychotic drug therapy and support for this boy and his family.

Choosing the most optimal treatment

Children and adolescents can have one or more psychiatric disorders or symptoms, including autism spectrum disorder, anxiety disorders, and behavioral disorders. Treatment generally consists of a combination of psychoeducation, behavioral and psychosocial interventions, and psychotherapy, but can also include pharmacotherapy, for example, with antipsychotic drugs. There has been a rising trend in the use of antipsychotic drugs for children and adolescents.[1–3] This rising trend may have been caused by a greater acceptance of antipsychotic drug use in children, increased knowledge and awareness due to more available clinical evidence, a demand for quick and affordable treatments, and limited effectiveness of other treatment options.[4] However, over the last years, the prevalence of use among this young population has stabilized, or even declined, in several countries, including the Netherlands.[1,5,6] This could be the effect of a greater awareness of the severe adverse drug reactions (ADRs) that may occur in children and adolescents. Nevertheless, antipsychotic drug use for Dutch children and adolescents appeared to be high compared to other European countries.[1,2]

Choosing the most optimal treatment for the individual child or adolescent and the decision to prescribe drugs involves several steps according to the 6-step model of the World Health Organization's (WHO) Guide to Good Prescribing (Figure 1).[7,8] First, the child or adolescent's problem has to be defined. Second, the therapeutic objective must be specified in consultation with the child or adolescent and the parents or caregivers, depending on the age of the child or adolescent. In the Netherlands, children from the age of 12 years have to consent to therapy and parents or caregivers have to consent to the therapy of their child until the age of 16 years, according to the Medical Treatment Contracts Act (Wet op de Geneeskundige Behandelingsovereenkomst; WGBO). Third, the available treatment options, which can be found in, for example, clinical practice guidelines (CPGs), have to be considered. Fourth, from these population-based treatment options the most suitable option for the individual child or adolescent has to be selected. This selection for the individual child or adolescent at hand takes into consideration the therapeutic objectives that were previously defined as well as the risk of developing ADRs, the monitoring of the effects, the frequency of drug intake, concomitantly used other drugs, comorbidities, and other specific patient characteristics. Fifth, information and instructions have to be given and clearly explained to the child or adolescent and the parents or caregivers. Last but not least, the treatment has to be monitored and evaluated for efficacy and the occurrence of possible ADRs, and whether the treatment is convenient for the child or adolescent. Subsequently, the treatment can be adjusted when necessary. Consultation about the treatment with the child or adolescent and the parents or caregivers and involving them is important for good prescribing. This makes shared decision making indispensable in every step. Good prescribing practice thus involves much more than just writing a prescription.

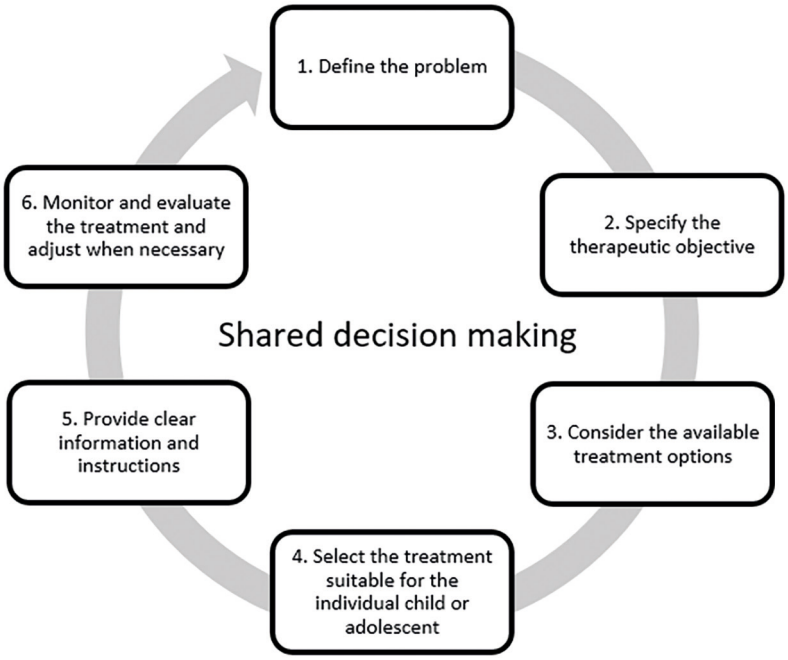


Figure 1. The 6-step model of the World Health Organization's Guide to Good Prescribing.[7,8]

Following these six steps may look simple on paper. In practice there are challenges in every step, especially when selecting a treatment and prescribing a drug for children or adolescents with a psychiatric disorder or symptoms. For example, for children and adolescents it is not always clear what the most suitable treatment is, as less evidence is available and less drugs are approved by the regulatory authorities for treatment in children and adolescents than for adults. Providing clear information and instructions to a child with an autism spectrum disorder will also be more challenging than providing instructions to an adult with hypertension. In addition, in practice, these steps do overlap. For example, when considering whether the treatment with a specific antipsychotic drug is suitable for the individual child or adolescent, the healthcare professional will possibly also provide information about this drug to the child or adolescent and parents or caregivers. This whole process also does not start or end with simply following these steps. Before the problem is defined, there has to be a signal that there actually is a problem. Furthermore, if the most suitable treatment is a drug, the child or adolescent, possibly with the help of a parent or caregiver, has to collect the drug from the pharmacy and start taking it as prescribed, and, subsequently, obtain a refill of the prescription once the drug is finished to continue taking the drug (Figure 2). This coincides with steps 5 and 6 (Figure 1). These steps continue until adjustment or discontinuation of the drug treatment after monitoring and evaluation. When the treatment has to be adjusted

or discontinued, a (possible) new problem has to be defined (Figure 1, step 1). The 6-step model of the WHO thus is a never ending cycle during the antipsychotic drug treatment of children and adolescents.

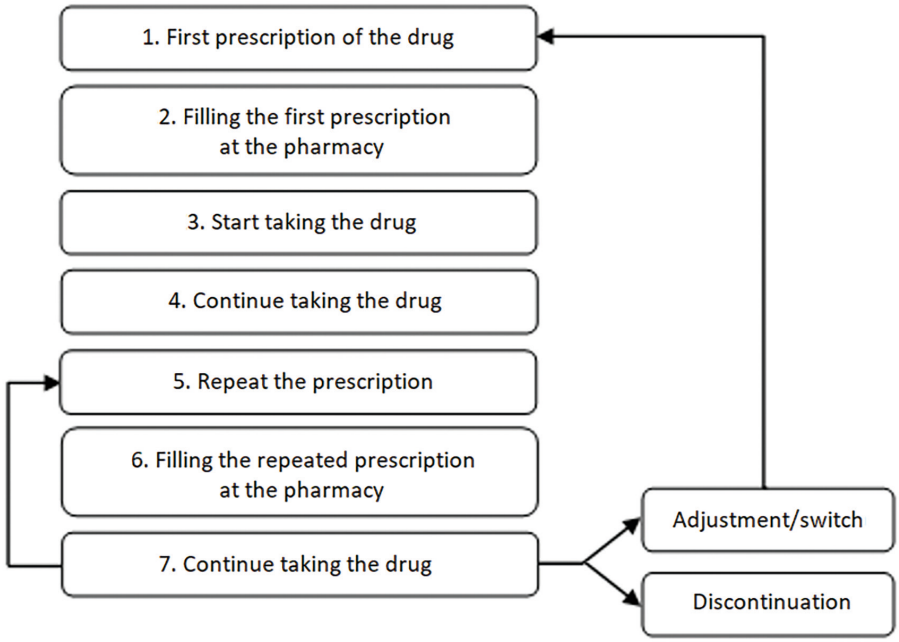


Figure 2. Cycle of drug taking.

Defining the problem of the individual child or adolescent

To define the problem or to diagnose a child or adolescent who displays psychiatric symptoms, in addition to the child or adolescent, the family or school teacher could be involved to form a total and more detailed overview of the problem to the healthcare professional, who, subsequently, makes a diagnosis by consideration of all the information received. This is an essential first step in the choice of the most optimal therapy for the child or adolescent.

Specifying the therapeutic objective for the individual child or adolescent

Once the problem is clear, or as clear as possible, the therapeutic objective can be identified. Specifying the therapeutic objective is not always easy in psychiatry. There are multiple therapeutic objectives other than "curing the patient." Regarding psychiatric symptoms, "cure" is often not possible nor desired. It is important to discuss the issue with the child or adolescent and the parents or caregivers to ascertain what they regard as important, their needs and preferences, and what

they want to achieve. For example, regarding the case described above, the autism will not disappear, but the boy can learn how to live with this diagnosis, and the aggressive behavior that affects the boy and his surroundings can be treated to become less of a burden.

Considering the available treatment options for children and adolescents

Options for the treatment of psychiatric disorders and symptoms include behavioral and psychosocial interventions and pharmacotherapy, as mentioned earlier. Healthcare professionals can consider the treatment options described in CPGs, but they may also consider prescribing a drug that they prescribe regularly and are familiar with. In the case described above, the child and adolescent psychiatrist suggests starting risperidone, which is an antipsychotic drug. Antipsychotic drugs can be prescribed to treat a variety of psychiatric disorders and symptoms, for example, irritability associated with autism, behavioral disorders, eating disorders, tic disorders, and attention-deficit/hyperactivity disorder (ADHD).[9,10] Although there is evidence for the efficacy of antipsychotic drugs in children and adolescents for some indications, including schizophrenia, bipolar disorder, and irritability with autism spectrum disorder, the evidence is limited.[10,11] The number of studies is low compared with studies in adults, there is a lack of head-to-head studies, and more randomized clinical trials are needed. Previous studies were mainly focused on the acute efficacy, so less is known about the long-term outcomes and safety. In addition, studies often do not represent daily clinical practice, as these studies are focused on one specific disorder, while in psychiatry children and adolescents can have multiple symptoms and (psychiatric) comorbidities. Nevertheless, antipsychotic drugs have been adopted in CPGs for the use in children and adolescents.[12,13] Antipsychotic drugs are approved by the regulatory authorities for the treatment of only few disorders and symptoms. In addition, not all antipsychotic drugs are approved for use in children and adolescents. For example, in the Netherlands, risperidone is only approved for short-term symptomatic treatment (up to 6 weeks) of persistent aggression in children (≥ 5 years old) and adolescents with a cognitive impairment and a diagnosis of a behavioral disorder.[14] Therefore, antipsychotic drugs are mostly prescribed off-label in children and adolescents.[15]

Although antipsychotic drugs can achieve a positive effect in children and adolescents, these drugs can also cause distressing and even severe ADRs. These ADRs can be cardiometabolic-related, including weight gain, abnormal blood glucose levels, abnormal blood lipid profile, hypertension, and tachycardia; endocrine-related, including gynecomastia, galactorrhea, or sexual dysfunction as a result of hyperprolactinemia; and extrapyramidal-related, including dyskinesia, akathisia, and parkinsonism.[16,17] In addition, antipsychotic drugs can cause several other ADRs, such as sedation and headaches. These ADRs can occur at all ages. However, the

occurrence and severity of ADRs can differ between adults and children, as, for example, children are at greater risk of severe weight gain and somnolence.[18,19] There needs to be a balance between the desired benefits of antipsychotic drug use and the potential harm the drugs may cause.

To learn more about the possible ADRs in a more vulnerable population for whom there is limited evidence available, such as children and adolescents, conducting clinical trials and cohort studies as well as the reporting of ADRs in a national system will be of great value. Through reporting, we learn more about the effects of antipsychotic drugs in children and adolescents in daily practice. We also learn more about the ADRs that may occur in the long term, as well as the rarer ones. In the Netherlands, we have "Bijwerkingencentrum Lareb," a national center that collects spontaneous reports of ADRs from patients and healthcare professionals, identifies risks, and provides information about the safety of drugs.[20] Furthermore, there is the Vigibase, the WHO's global database of individual case safety reports, which collects reports of suspected ADRs of drugs.[21] These reports have been submitted by member countries worldwide since 1968, and there are currently over 20 million reports. These databases provide valuable information on the potential ADRs and the safety of antipsychotic drugs in children and adolescents in daily practice. Information that is, most often, missing is trials.

Selecting the treatment suitable for the individual child or adolescent

After defining the available treatment options, the most suitable option for the individual child or adolescent at hand has to be selected. In the described case, the child and adolescent psychiatrist suggests prescribing risperidone after psychosocial guidance was insufficient for the treatment of aggressive behavior in a boy who had been diagnosed with autism spectrum disorder. When initiating antipsychotic drugs, it is never clear whether the desired positive effect will be achieved and which ADRs may occur. Therefore, prescribing these drugs to a child or adolescent may be an n = 1 experiment. Different aspects have to be considered to verify whether this treatment is suitable. First, the treatment outcome has to align with the previously defined therapeutic objectives. In addition, the prospect of a positive effect, the risks of developing ADRs, and the need for monitoring are important aspects to consider. One of the possible ADRs is weight gain. As the boy described in the case is already overweight, it is probably even more important to monitor the weight of the child. The child and adolescent psychiatrist also wants to monitor the glucose, cholesterol, and prolactin blood levels. However, the boy has a fear of needles, and even though they do not want the monitoring to be a burden, it also cannot be ignored. There should be a balance between the desired positive effect, the safety of the drug regarding possible ADRs, and the burden of monitoring. Other aspects that have to be clarified to determine whether a treatment is suitable for an individual

child or adolescent are, for example, the dosage schedule and additional specific patient characteristics, such as diseases in the family history and comorbidities such as diabetes mellitus or a long QT syndrome. In the determination of the right dosage, it has to be considered that children cannot simply be regarded as small adults. Developmental changes at a young age can alter the pharmacokinetics and pharmacodynamics, and growth is not a linear process.[22] All the aspects mentioned here emphasize the need for a therapy suitable for and tailored to an individual child or adolescent.

When prescribing an antipsychotic drug to a child or adolescent, not only the effects, safety, monitoring, and schedule of the drug treatment have to be considered but also the impact on the daily life of the child or adolescent. The development of a child or adolescent is a continuous process, which involves not only physical growth but also cognitive, emotional, social, and behavioral changes. The ADRs that may occur do not only have physical consequences, as described earlier, but can also have an emotional impact. For example, the development of overweight or gynecomastia can have a great impact on the self-confidence and self-image of an adolescent. The development of ADRs as well as the continuous monitoring for ADRs can impact quality of life, as children can have a fear of needles, as mentioned earlier, but also because the monitoring is a constant reminder that they have to use drugs to treat a disorder or symptom. Children and adolescents may be ashamed of their antipsychotic drug use and of the occurred ADRs. A previous study has shown that stigmatization may influence their young lives.[23] This can have a great impact on their social development, which is important at young age.

Providing clear information and instructions regarding the antipsychotic drug treatment

Before the start of and during treatment, the child or adolescent should be involved in the decision making and given clear information and instructions regarding the therapy. In the Netherlands, children from the age of 12 years have to consent to therapy, according to the Medical Treatment Contracts Act. Therefore, it is important to provide them with clear information regarding their therapy. In addition, with antipsychotic drug treatment, clear information and instructions are also important so that the child or adolescent will know how to use the drug and what to expect, in consideration of the impact that antipsychotic drug use and the monitoring can have physically as well as emotionally and socially. Supporting this vulnerable population can be more difficult and more challenging than, for example, a child with asthma or an adult with a high blood pressure, because of the possible impact of the disorder or symptoms on the child or adolescent and his or her surroundings as well as the impact this treatment, including the monitoring, can cause.

Similar to the selected treatment, the support must be suitable for and tailored to the individual child or adolescent and the parents or caregivers. Previous work of our group showed that the content, communication, and organization of the guidance are important to achieve optimal support.[24] When a drug is prescribed, tailored information has to be provided regarding the effects, possible ADRs, the use of the drug, the required monitoring of the effects, why monitoring is necessary, and potential warnings. In addition, the child or adolescent may have a variety of questions that need to be answered before the treatment is commenced, for example, "Does it cause many adverse effects?" More and different questions may arise during the antipsychotic drug treatment, for example, "Can I ever stop using this drug and how do I taper it off?" or "Can this drug cause these sexual side effects?" Previous studies have shown that the support provided to patients or caregivers is not always optimal.[23–25] The support provided to the children and adolescents treated with antipsychotic drugs as well as to the parents or caregivers should correlate with their level of knowledge and individual needs and preferences. Personalized support may help them to understand what to expect, and why and how they have to take the drug. This will help to increase compliance with the therapy, to achieve the maximum positive effect, and to reduce the burden of the treatment for the child or adolescent.

Monitoring, evaluation, and adjustment of the antipsychotic drug treatment

Monitoring of the treatment is essential to evaluate the positive as well as the negative effects that may occur and to adjust the therapy as necessary. With carefully monitoring and evaluation of the benefits and harms in each individual child and adolescent, the balance can be maintained on the positive side. Monitoring for ADRs at the start of and during antipsychotic drug treatment is important to ensure drug safety. Cardiometabolic, endocrine, and extrapyramidal adverse effects can be monitored through related physical (e.g., weight, height, body mass index [BMI], blood pressure, and pulse), laboratory (e.g., blood glucose, lipids, and prolactin levels), and observational (e.g., movement disorders and the development of gynecomastia) parameters (Table 1).[13,26,27] Children and adolescents can also answer questions about the development of extrapyramidal effects or ADRs related to hyperprolactinemia, as well as about, for example, sedation or headache. Regular monitoring and evaluation can lead to the early detection of ADRs. Subsequently, therapy can be either continued with extra care, discontinued, switched, or adjusted timeously to maintain drug safety for the individual child or adolescent.

Table 1. Examples of monitoring for adverse drug reactions caused by antipsychotic drugs.[13,14,26,27]

Adverse drug reactions	Monitoring
Metabolic adverse effects Weight gain Abnormalities in blood glucose Abnormalities in blood lipids	Weight Body mass index Waist and hip circumference Blood lipid profile Blood glucose Hemoglobin A1c
Cardiovascular adverse effects Hypertension Cardiac arrhythmias Prolonged QTc-interval	Blood pressure Pulse Electrocardiogram
Endocrine adverse effects Hyperprolactinemia Gynecomastia Galactorrhea Sexual dysfunction Menstrual irregularities	Blood prolactin Observational Questionnaire
Extrapyramidal adverse effects Parkinsonism Akathisia Dyskinesia Tremor	Observational Questionnaire

Advice and instructions on the monitoring of children and adolescents treated with antipsychotic drugs for ADRs are described in CPGs as well as in the Summary of Product Characteristics (SmPC) of the specific antipsychotic drugs.[13,14,26–30] The instructions included in the CPG or SmPC have to be clearly presented and easily applicable for use in daily clinical practice. However, previous studies of our group have shown that instructions are not always clearly described and, especially, not easily applicable in daily clinical practice.[31–33] The overall CPG should be clear, for example, on where to find the monitoring instructions, what the barriers and facilitators are, and how to put the instructions into practice.[34] In addition, the individual monitoring instructions described in the CPGs have to be clear and applicable. It should at least describe why it is important to monitor an ADR-related parameter, what to monitor, when to start and stop monitoring, the frequency of monitoring, what to look for or what the critical values are, and how to respond to abnormalities.[35] On the one hand, when the clarity of a CPG is sufficient and the monitoring instructions are easily applicable in daily clinical practice, the CPG can be a facilitator in the monitoring for ADRs in children and adolescents treated with antipsychotics drugs to achieve drug safety. On the other hand, the lack of such a CPG may be one of the barriers to achieving drug safety in this young and vulnerable population.

Although monitoring for ADRs in children and adolescents treated with antipsychotic drugs contributes to drug safety, previous studies have shown that actual monitoring frequencies are suboptimal.[36,37] Children and adolescents also seem to be less likely to have laboratory monitoring than adults.[38] However, it is not clear what "optimal" monitoring actually means. Therefore, there is no simple answer to the question posed by the child and adolescent psychiatrist described in the case above, who wonders what the most optimal way of monitoring is for this boy, taking into account his overweight and fear of needles. Before a drug is approved by the regulatory authorities and enters the market, there are several research phases that have to be completed to obtain evidence for efficacy and safety, including preclinical and clinical research. Still, there is no clear evidence available regarding which ADR-related parameters should definitely be monitored to ensure drug safety and the frequency of monitoring. This increases the complexity of defining how children and adolescents should be monitored at the start of and during antipsychotic drug treatment.

Even though the most optimal way of monitoring is not completely clear, severe ADRs can occur, and children and adolescents should be monitored to prevent or reduce any possible harm. However, there may be barriers to monitoring. The lack of clear CPGs can be a barrier to monitoring, but there could also be a variety of other barriers that cause low monitoring numbers. Some of the reasons can be related to the healthcare professionals, including a lack of time, a lack of awareness or knowledge, a lack of equipment, or poor collaboration between healthcare professionals.[39,40] Although antipsychotic drugs are most often prescribed by (child and adolescent) psychiatrists, other healthcare professionals, for example, general practitioners, can also be involved in the monitoring of antipsychotic drug therapy.[3] Therefore it should be clear who is responsible for monitoring for ADRs. However, in daily clinical practice, this does not always seem to be the case.[40,41] In addition, barriers to monitoring can also be related to the parents or caregivers, who can refuse or simply forget to take a test, or the children and adolescents, due to, for example and as also mentioned in the case described above, a fear of needles.[42,43] By recognizing barriers, these can be addressed to improve monitoring practices.

Shared decision making

During this entire process, from identifying the problem to evaluating the therapy, shared decision making is essential. Shared decision making means that both the healthcare professional and the child or adolescent, and, potentially, the parents or caregivers, are involved in the decision making.[44] They all bring their own expertise. The healthcare professional has expertise in antipsychotic drug treatment, including the potential benefits and risks, and the child or adolescent has expertise related to their values, needs, and preferences.[44] Shared decision making will be more challenging when there is a child with autism involved who developed aggressive

behavior than, for example, an adult with diabetes mellitus. But still, without hearing the voice of the children and adolescents, as well as the voice of the parents or caregivers, the healthcare professional may miss essential information to make clinical decisions. For the children and adolescents, discussing the therapy with their healthcare professional, if they are able, could lead to a better understanding of their own therapy, including why it is important to monitor. Subsequently, a better understanding could lead to a greater acceptance of the antipsychotic drug treatment.

Knowledge gap

Although less is known about the efficacy of antipsychotic drugs in children and adolescents compared with adults, it is known these drugs are frequently prescribed to this young population and can cause severe and bothersome ADRs. Therefore, monitoring is essential for a safe use of antipsychotic drugs. However, it is unclear what actually is done in daily clinical practice regarding monitoring for the ADRs in children and adolescents. Previous studies have shown suboptimal monitoring frequencies for several drugs and different patient groups but the facilitators and barriers of monitoring remain unclear.[36,45,46] Questions arise what the considerations are for not monitoring, whether the monitoring instructions included in CPGs for children and adolescents treated with antipsychotic drugs are clear and applicable in daily clinical practice, and what the needs and preferences are from children, adolescents, parents, and caregivers regarding the support from healthcare professionals. By learning more about monitoring for ADRs of antipsychotic drugs in daily practice, the monitoring of and care for this young and vulnerable population can be improved where necessary to ensure a safe antipsychotic drug use.

Objective of this thesis

The overall aim of this thesis is to assess the daily clinical practice of monitoring for ADRs of antipsychotic drugs in children and adolescents, including the facilitators for and barriers to monitoring. This aim was divided into the following objectives:

- To determine the need for monitoring for ADRs in children and adolescents treated with antipsychotic drugs;
- To examine monitoring of ADR-related parameters in children and adolescents treated with antipsychotic drugs by healthcare professionals in daily clinical practice;
- To assess the support provided to healthcare professionals and to the children and adolescents regarding monitoring for ADRs of antipsychotic drugs.

Outline of this thesis

Chapter 2 focuses on the need for monitoring for ADRs in children and adolescents treated with antipsychotic drugs. **Chapter 2.1** provides an overview of spontaneously reported ADRs by the children, adolescents, parents, caregivers, and healthcare professionals.

Chapter 3 examines monitoring by healthcare professionals in daily clinical practice. **Chapter 3.1** focuses on how healthcare professionals report on monitoring for ADRs in children and adolescents treated with antipsychotic drugs. In **Chapters 3.2** and **3.3**, we focus on how this young population is actually monitored in daily clinical practice, by assessing the medical records of children and adolescents treated in psychiatric outpatient clinics and a database with medical records of general practices.

Chapter 4 addresses the support provided regarding antipsychotic drug use, including monitoring. **Chapter 4.1** focuses on the support provided to healthcare professionals. This chapter presents an evaluation of ADR-related monitoring instructions in CPGs for children and adolescents treated with antipsychotic drugs, whereby the clarity and applicability are assessed. **Chapter 4.2** focuses on the support provided to adolescents by healthcare professionals during antipsychotic drug treatment, and their needs, preferences, and suggestions for improvement.

Finally, in **Chapter 5**, the results of previous chapters are put into a broader perspective in the general discussion.

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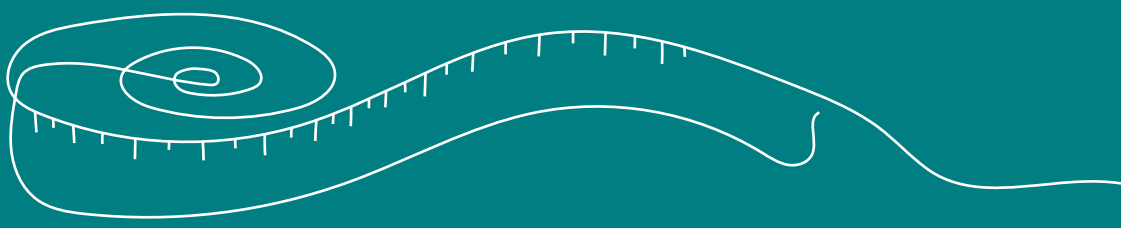

Chapter 2

Need for monitoring

Chapter 2.1

Reported adverse drug reactions in children and adolescents treated with antipsychotics

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ABSTRACT

Objectives

To characterize reported adverse drug reactions (ADRs) in children and adolescents treated with antipsychotics and determine differences in relative reporting frequency between genders, age classes, and reporter types.

Methods

Individual case safety reports of children ages 1 - 17 years in whom an antipsychotic drug was the suspected or interacting drug from the worldwide database, VigiBase, from 1968 until March 2017, were included. Reported ADRs were categorized based on the Standardized Medical Dictionary for Regulatory Activities (MedDRA) Queries and clinical reasoning. Proportional reporting ratios (PRRs) and 95% confidence intervals (95% CIs) were calculated for genders, age classes, and reporter types.

Results

In total, 45,201 reported ADRs were included. The most frequently reported were ADRs related to extrapyramidal syndrome (14.7%), breast disorders or blood prolactin level changes (4.7%), and cardiac arrhythmias (4.6%). Differences in relative reporting frequencies were observed between age classes and reporter types, and less prominent between genders. For example, ADRs related to hyperglycemia/new-onset diabetes mellitus were less frequently reported in children ages 1 - 5 than in children ages 12 - 17 (PRR: 0.4, 95% CI: 0.2 - 0.5). ADRs related to cardiac arrhythmias were less frequently reported by consumers compared with health care professionals (PRR: 0.5, 95% CI: 0.5 - 0.6), whereas ADRs related to a change in weight/body mass index were more frequently reported by consumers (PRR: 3.2, 95% CI: 2.9 - 3.5).

Conclusion

A wide spectrum of ADRs were reported in children treated with antipsychotics. The relative differences in reporting frequency between age classes and reporter types can be of help to tailor information about possible ADRs and to monitor for ADRs.

INTRODUCTION

Antipsychotics are frequently prescribed to children and adolescents (hereafter referred to as children) to treat psychiatric disorders, including disruptive behavior disorder, autism spectrum disorder, and attention-deficit/hyperactivity disorder.[1,2] Despite the frequent use in this young population, the evidence for the efficacy and safety of antipsychotic treatment in children is scarce and off-label prescribing is common.[3] This is of concern because of the seriousness of adverse effects, the lack of knowledge of long-term effects, and the vulnerability of this population.

Effects of antipsychotics have mostly been studied in adults.[4] However, the efficacy and safety outcomes of studies in adults cannot easily be extrapolated to children.[5–8] Developmental changes in children concerning gastrointestinal function, metabolic capacity, and renal function, and the inter- and intraindividual variability in pharmacokinetics require individualized dosing of antipsychotics.[5] In addition, effects of antipsychotics in children can differ from those in adults. For example, children treated with antipsychotics have a greater risk of weight gain and somnolence compared with adults.[9,10] Also, the perceived severity of adverse drug reactions (ADRs) in children may differ from that in adults. For example, hyperprolactinemia may be more distressing to adolescents because it can cause a delay in pubertal maturation, menstrual disturbances, gynecomastia, and sexual dysfunction.[11] In this study, not only age but also gender may play a role, as adolescent females treated with antipsychotics may be more prone to experience greater changes in prolactin levels than males.[12,13]

Although studies have looked into specific ADRs in children, an overview of the (reported) occurrence frequencies of ADRs in children treated with antipsychotics is missing. Reporting systems of ADRs are a valuable source by which to obtain such an overview and to gain knowledge on the safety of antipsychotic drug use in children. Most countries have a national reporting system in which both health care professionals and patients report suspected ADRs, which are subsequently collected in the World Health Organization's (WHO) global database of individual case safety reports (ICSRs), VigiBase.[14] It is unknown which ADRs are reported in children treated with antipsychotics and also who reports these ADRs.

The aim of this study was to characterize reported ADRs in children treated with antipsychotics and determine differences in relative reporting frequency between genders, age classes, and reporter types.

METHODS

Setting

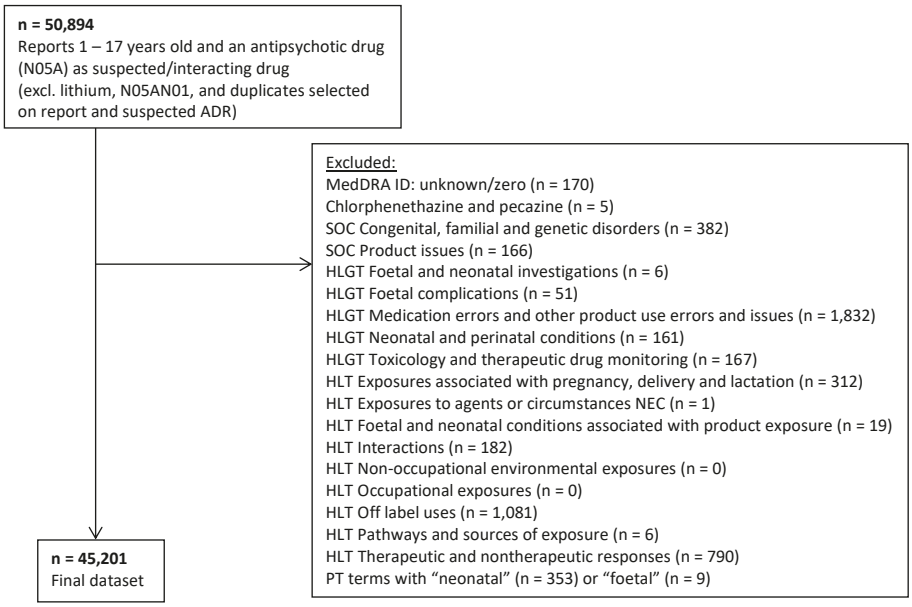
This study was conducted using data from VigiBase, the WHO global ICSR database.[14] In the aftermath of the thalidomide disaster in the early 1960s, the WHO Programme for International Drug Monitoring was established in 1968. In each country participating in this program, a national center for pharmacovigilance collects and manages spontaneous reports of suspected ADRs, for instance, by health care professionals or patients themselves. These ICSRs are sent to the Uppsala Monitoring Centre (UMC) — the WHO Collaborating Centre for International Drug Monitoring — in Sweden, which maintains the reports in VigiBase. Information available in the ICSRs includes patient demographics, suspected drugs, reported ADRs, and additional information relevant to the case.[14] Reported ADRs are coded at the originating national center, either according to the WHO Adverse Reaction Terminology (WHO-ART) or the Medical Dictionary for Regulatory Activities (MedDRA).[14] VigiBase uses both WHO-ART and MedDRA; for this study MedDRA was used. Suspected drugs recorded on the ICSRs are coded according to the WHO Drug Dictionary.[14] In 2017, VigiBase contained more than 16 million ICSRs, originating from more than 120 member countries.[15,16]

Selection of ADRs

Included in this study were all ICSRs that were notified since the establishment of VigiBase in 1968 until March 2017 concerning children ages 1 – 17 years, in whom an antipsychotic (ATC code N05A, excluding lithium [N05AN01]) was the suspected or interacting drug (Figure 1).

Children ages <1 year and the MedDRA terms, including “neonatal” or “foetal,” were excluded, as the reported ADR in such cases was probably related to the use of an antipsychotic by the mother and not by the child itself. As not all reported MedDRA terms were ADRs, the terms in Figure 1 were excluded. Each MedDRA term has a unique MedDRA code; ICSRs without a valid MedDRA code and duplicate MedDRA codes in one ICSR were excluded.

Figure 1. Flowchart of the process of selection of adverse drug reactions.



ADR, adverse drug reaction; HLGT, high-level group term; HLT, high-level term; MedDRA, Medical Dictionary for Regulatory Activities; n, number of reported adverse drug reactions; PT, preferred term; SOC, system organ class.

Classification of ADRs

The unit of analysis was the reported ADR (MedDRA code). Reported ADRs were categorized according to system organ classes (SOCs) and subsequently based on Standardized MedDRA Queries (SMQs) and clinical reasoning.

The MedDRA hierarchy was used to evaluate the reported ADRs in the ICSRs. The MedDRA hierarchy consists of five levels: lowest level terms (LLTs), preferred terms (PTs), high-level terms (HLTs), high-level group terms (HLGTs), and SOCs. All reported MedDRA terms were either PTs or LLTs. Both PTs and LLTs can be linked to more than one SOC, but there is always a primary SOC. The primary SOC is the prime manifestation site if the PT or LLT relates to a disease or symptom.[17] For this study, only the primary SOCs were used (Supplementary Table S1 and Supplementary Figure S1).

Different ADRs can be reported for the same disease or symptom. These ADRs were combined into one group based on SMQs and clinical reasoning. SMQs are validated groups of MedDRA terms that relate to the same medical condition or area of interest.[17] For the SMQs, narrow scope terms were used, but if in our opinion the broad scope terms comprised crucial ADRs that needed to be included in this

study, these were used. The narrow scope terms are more specific, whereas the broad scope terms are more sensitive and include narrow terms and terms of less specific nature.[18] Reported terms can contribute to more than one SMQ; for instance, *oculogyric crisis* was attributed to the SMQs: e*xtrapyramidal syndrome* and *ocular motility disorders*. Due to this overlap, the numbers of reported ADRs (or MedDRA terms) in different SMQs cannot be combined to calculate the total number of reported ADRs (Table 1 and Figure 2). If no SMQ was available for terms related to the same medical condition, HLGTs, HLTs, and PTs were included based on clinical reasoning. The final overview was discussed and resolved by consensus with two additional authors (T.C.G.E., E.R.H.).

Data analysis

Descriptive statistics were used to obtain an overview of the most frequently reported ADRs. Data were stratified by gender, age and reporter type. Age was stratified into three age classes: 1 – 5, 6 – 11, and 12 – 17 years old. Reporter types were stratified into health care professionals and consumers. The former included the reporter types "physician," "pharmacist," "other health professional," "general practitioner," "specialist physician," "dentist," "nurse," and "hospital," while the latter included the reporter types "consumer/non-health professional" and "other."

The relative reporting frequencies were calculated and expressed as a percentage of the total reported ADRs and of the total reported ADRs in males, females, consumers, health care professionals, or age classes. The ratios of the reported ADRs for males versus females, consumers versus health care professionals, and between age classes were expressed as proportional reporting ratios (PRRs) and 95% confidence intervals (95% CIs). The PRR was based on a two-by-two contingency table:

$$PRR = [a/(a+b)] / [c/(c+d)]$$

where a and c denote the reported ADRs among males and females, respectively, among consumers and health care professionals, respectively, or among age classes; (a+b) and (c+d) denote the total reported ADRs among males and females, respectively, among consumers and health care professionals, respectively, or among age classes.

All statistical analyses were performed using SPSS Statistics version 24.

RESULTS

In this study, 18,950 unique ICSRs containing 45,201 reported ADRs were included of children ages 1 – 17 years with an antipsychotic drug as the suspected or interacting drug (Figure 1). There was an average of 2.4 reported ADRs per ICSR. In total, 61 different (generic) antipsychotic drugs were included in the ICSRs, through which 1 ICSR could include more than 1 antipsychotic drug. The most frequently reported suspected antipsychotic drug was risperidone (n = 5,321 ICSRs), followed by aripiprazole (n = 3,687 ICSRs) and quetiapine (n = 2,183 ICSRs).

When categorizing according to SMQs and clinical reasoning, the most frequently reported ADRs (Table 1) were related to extrapyramidal syndrome (n = 6,630; 14.7%), breast disorders or blood prolactin level changes (n = 2,131; 4.7%), cardiac arrhythmias (n = 2,080; 4.6%), disturbances in consciousness (n = 2,073; 4.6%), and change in weight/body mass index (BMI; n = 1,959; 4.3%); together comprising one-third (32.3%) of all reported ADRs. ADRs related to a change in weight/BMI mostly regarded an increase (n = 1,811; 92.4%) and less often regarded a decrease (n = 132; 6.7%) or other (e.g., weight fluctuation; n = 16; 0.8%). The results of categorizing according to SOCs are shown in Supplementary Table S1 and Supplementary Figure S1.

ADRs stratified according to gender

In total, 27,536 (60.9%) ADRs were reported in males, 16,654 (36.8%) in females, and for 1,011 (2.2%) ADRs the gender was unknown (Table 1). The relative reporting frequencies differed between males and females. Concerning psychiatry-related ADRs, those related to depression and suicide/self-injury (2.3% vs. 4.4%; PRR: 0.5, 95% CI: 0.5 – 0.6), and drug abuse, dependence, and withdrawal (0.9% vs. 1.3%; PRR: 0.7, 95% CI: 0.6 – 0.8) were relatively less frequently reported in males than in females, whereas those related to hostility/aggression (2.2% vs. 1.4%; PRR: 1.6, 95% CI: 1.4 – 1.8) were relatively more frequently reported in males than in females. Other ADRs that were relatively more frequently reported in males were those related to a change in weight/BMI (4.8% vs. 3.5%; PRR: 1.4, 95% CI: 1.2 – 1.5) and breast disorders or blood prolactin level changes (5.2% vs. 4.1%; PRR: 1.2, 95% CI: 1.1 – 1.4). For the latter, the most frequently reported ADR in males was *gynecomastia* (*n* = 832; 58.3%), while in females it was *galactorrhea* (*n* = 300; 43.5%).

Table 1. Most reported adverse drug reactions categorized by Standardized Medical Dictionary for Regulatory Activities Queries and clinical reasoning.

	Three most reported adverse drug reactions (n)	Total	Gender			Age (years old)				
		n = 45,201	Male n = 27,536	Female n = 16,654	Male/Female	1 – 5 n = 3,232	1-5/12-17	6 – 11 n = 11,296	6-11/12-17	12 – 17 n = 30,673
		%	%	%	PRR [95%CI]	%	PRR [95%CI]	%	PRR [95%CI]	%
Neurological										
Extrapyramidal syndrome[1]	Dystonia (1,095), extrapyramidal disorder (949), dyskinesia (664)	14.7	15.2	13.7	**1.1 [1.1-1.2]**	14.8	1.1 [1.0-1.2]	16.8	**1.2 [1.1-1.3]**	13.9
Disturbances in consciousness NEC[2]	Somnolence (1,037), sedation (350), lethargy (194)	4.6	4.3	4.9	**0.9 [0.8-0.9]**	8.3	**2.0 [1.7-2.2]**	4.5	1.1 [1.0-1.2]	4.2
Convulsions[3]	Seizure (521), generalised tonic-clonic seizure (115), epilepsy (47)	1.7	1.5	1.8	**0.9 [0.7-1.0]**	2.4	**1.6 [1.2-2.0]**	1.7	1.1 [0.9-1.3]	1.6
Asthenic conditions[2]	Fatigue (333), malaise (153), asthenia (119)	1.4	1.4	1.5	1.0 [0.8-1.1]	1.1	0.7 [0.5-1.0]	1.4	0.9 [0.8-1.1]	1.5
Ocular motility disorders[3]	Oculogyric crisis (334), eye movement disorder (105), nystagmus (26)	1.2	1.1	1.4	**0.8 [0.7-1.0]**	1.7	**1.4 [1.1-1.9]**	1.3	1.1 [0.9-1.3]	1.2
Psychiatric										
Psychosis and psychiatric disorders[1]	Abnormal behaviour (294), hallucination (196), psychotic disorder (182)	3.7	3.8	3.8	1.0 [0.9-1.1]	2.7	**0.7 [0.6-0.9]**	4.0	1.0 [0.9-1.2]	3.8
Depression and suicide / self-injury[3]	Suicide attempt (343), suicidal ideation (277), intentional overdose (216)	3.2	2.3	4.4	**0.5 [0.5-0.6]**	0.5	**0.1 [0.1-0.2]**	1.8	**0.4 [0.4-0.5]**	4.0

Table 1. Continued

	Three most reported adverse drug reactions (n)	Total	Gender			Age (years old)				
		n = 45,201	Male n = 27,536	Female n = 16,654	Male/Female	1 – 5 n = 3,232	1-5/12-17	6 – 11 n = 11,296	6-11/12-17	12 – 17 n = 30,673
		%	%	%	PRR [95%CI]	%	PRR [95%CI]	%	PRR [95%CI]	%
Anxiety disorders and symptoms[4]	Agitation (478), anxiety (247), nervousness (55)	2.2	2.1	2.4	0.9 [0.8-1.0]	2.3	1.1 [0.9-1.4]	2.5	**1.2 [1.0-1.3]**	2.1
Hostility / aggression[3]	Aggression (575), anger (157), homicidal ideation (33)	1.9	2.2	1.4	**1.6 [1.4-1.8]**	1.4	0.9 [0.7-1.3]	2.9	**1.9 [1.7-2.2]**	1.5
Sleep disorders and disturbances[4]	Insomnia (272), sleep disorder (90), nightmare (40)	1.1	1.0	1.2	**0.8 [0.7-1.0]**	1.1	1.1 [0.7-1.5]	1.3	**1.2 [1.0-1.5]**	1.0
Drug abuse, dependence and withdrawal[3]	Intentional overdose (216), drug withdrawal syndrome (95), intentional product misuse (90)	1.1	0.9	1.3	**0.7 [0.6-0.8]**	0.7	**0.6 [0.4-0.8]**	0.5	**0.4 [0.3-0.5]**	1.3
Gastointestinal and hepatic										
Gastrointestinal nonspecific inflammation and dysfunctional conditions[3]	Vomiting (504), nausea (368), constipation (139)	3.3	3.1	3.6	**0.9 [0.8-1.0]**	3.4	1.0 [0.9-1.3]	3.4	1.1 [0.9-1.2]	3.2
Oropharyngeal disorders[3]	Salivary hypersecretion (283), swollen tongue (70), dry mouth (67)	2.1	2.1	2.1	1.0 [0.9-1.2]	1.5	**0.7 [0.5-0.9]**	2.0	0.9 [0.8-1.1]	2.2

Table 1. Continued

	Three most reported adverse drug reactions (n)	Total	Gender			Age (years old)				
		n = 45,201	Male n = 27,536	Female n = 16,654	Male/Female	1 – 5 n = 3,232	1-5/12-17	6 – 11 n = 11,296	6-11/12-17	12 – 17 n = 30,673
		%	%	%	PRR [95%CI]	%	PRR [95%CI]	%	PRR [95%CI]	%
Hepatic disorders[3]	Alanine aminotransferase increased (116), hepatic function abnormal (110), aspartate aminotransferase increased (108)	1.8	2.0	1.6	**1.3 [1.1-1.5]**	1.0	**0.5 [0.3-0.7]**	1.4	**0.7 [0.6-0.8]**	2.1
Endocrine and metabolic										
Breast disorders[4] and blood prolactin level changes[5a]	Gynaecomastia (849), hyperprolactinaemia (489), galactorrhoea (402)	4.7	5.2	4.1	**1.2 [1.1-1.4]**	1.5	**0.3 [0.2-0.4]**	5.0	1.0 [0.9-1.1]	5.0
Change in weight / Body Mass Index[5b]	Weight increased (1,316), abnormal weight gain (326), obesity (142)	4.3	4.8	3.5	**1.4 [1.2-1.5]**	2.0	**0.5 [0.4-0.7]**	6.1	**1.5 [1.4-1.7]**	3.9
Hyperglycaemia / new onset diabetes mellitus[3]	Diabetes mellitus (incl. Type 1 and 2) (348), hyperglycaemia (127), blood glucose increased (91)	1.8	1.7	2.0	0.9 [0.8-1.0]	0.6	**0.4 [0.2-0.5]**	2.0	1.1 [0.9-1.3]	1.8
Other										
Cardiac arrhythmias[1]	Tachycardia (610), electrocardiogram QT prolonged (224), loss of consciousness (143)	4.6	4.4	4.9	**0.9 [0.8-1.0]**	4.5	0.9 [0.7-1.0]	3.2	**0.6 [0.6-0.7]**	5.1

Table 1. Continued

	Three most reported adverse drug reactions (n)	Total	Gender			Age (years old)				
		n = 45,201	Male n = 27,536	Female n = 16,654	Male/Female	1 – 5 n = 3,232	1-5/12-17	6 – 11 n = 11,296	6-11/12-17	12 – 17 n = 30,673
		%	%	%	PRR [95%CI]	%	PRR [95%CI]	%	PRR [95%CI]	%
Haematopoietic cytopenias[3]	Leukopenia (370), neutropenia (286), granulocytopenia (262)	3.2	3.2	3.1	1.0 [0.9-1.1]	1.8	**0.5 [0.4-0.6]**	1.9	**0.5 [0.4-0.6]**	3.8
Hypersensitivity[3]	Rash (253), urticaria (90), swollen tongue (70)	2.6	2.6	2.6	1.0 [0.9-1.1]	1.9	**0.7 [0.6-1.0]**	2.7	1.1 [0.9-1.2]	2.6
Body temperature conditions[4] and body temperature[5c]	Pyrexia (399), body temperature increased (48), hypothermia (40)	1.2	1.3	1.2	1.0 [0.9-1.2]	1.6	1.3 [0.9-1.7]	0.9	**0.7 [0.6-0.9]**	1.3
Breathing abnormalities[2] and respiratory rate[5d]	Dyspnoea (267), respiratory arrest (55), respiratory distress (47)	1.2	1.2	1.1	1.1 [0.9-1.3]	2.5	**2.4 [1.9-3.0]**	1.2	1.1 [0.9-1.4]	1.1
Urinary tract signs and symptoms[4]	Urinary incontinence (152), urinary retention (90), dysuria (41)	1.0	1.1	0.9	**1.3 [1.1-1.6]**	0.6	**0.6 [0.3-0.9]**	1.1	1.0 [0.8-1.3]	1.1

1. SMQ broad terms (MedDRA); 2. High-Level Term (HLT); 3. SMQ narrow terms; 4. High-Level Group Term (HLGT); 5a. PT: blood prolactin, blood prolactin abnormal, blood prolactin decreased, blood prolactin increased, hyperprolactinaemia, hypoprolactinaemia; 5b. PT: abnormal loss of weight, abnormal weight gain, body mass index increased, obesity, overweight, underweight, weight, weight abnormal, weight decreased, weight fluctuation, weight gain poor, weight increased; 5c. PT: body temperature decreased, body temperature fluctuation, body temperature increased; 5d. PT: breath sounds abnormal, respiratory rate decreased, respiratory rate increased.
Bold values indicate significant difference.
MedDRA, Medicinal Dictionary for Regulatory Activities; n, number of reported adverse drug reactions; NEC, not elsewhere classified; PRR [95%CI], proportional reporting ratio [95% confidence interval]; PT, Preferred Term; SMQ, Standardized MedDRA Query.

ADRs stratified according to age class

In total, 3,232 (7.2%) ADRs were reported in children ages 1 – 5, 11,296 (25.0%) in children ages 6 – 11, and 30,673 (67.9%) in children ages 12 – 17 (Table 1). The relative reporting frequencies differed between age classes.

Concerning neurology-related ADRs, those related to disturbances in consciousness (8.3% vs. 4.2%; PRR: 2.0, 95% CI: 1.7 – 2.2) and convulsions (2.4% vs. 1.6%; PRR: 1.6, 95% CI: 1.2 – 2.0) were relatively more frequently reported in children ages 1 – 5 than in children ages 12 – 17.

Concerning psychiatry-related ADRs, those related to depression and suicide/self-injury (0.5% vs. 4.0%; PRR: 0.1, 95% CI: 0.1 – 0.2), and drug abuse, dependence, and withdrawal (0.7% vs. 1.3%; PRR: 0.6, 95% CI: 0.4 – 0.8) were relatively less frequently reported in children ages 1 – 5 than in children ages 12 – 17, and also relatively less frequently in children ages 6 – 11 than in children ages 12 – 17 (1.8% vs. 4.0%; PRR: 0.4, 95% CI: 0.4 – 0.5 and 0.5% vs. 1.3%; PRR: 0.4, 95% CI: 0.3 – 0.5, respectively). ADRs related to hostility/aggression were relatively more frequently reported in children ages 6 – 11 than in children ages 12 – 17 (2.9% vs. 1.5%; PRR: 1.9, 95% CI: 1.7 – 2.2).

Concerning endocrine- and metabolism-related ADRs, those related to breast disorders or blood prolactin level changes (1.5% vs. 5.0%; PRR: 0.3, 95% CI: 0.2 – 0.4) and hyperglycemia/new-onset diabetes mellitus (0.6% vs. 1.8%; PRR: 0.4, 95% CI: 0.2 – 0.5) were relatively less frequently reported in children ages 1 – 5 than in children ages 12 – 17. ADRs related to a change in weight/BMI were also relatively less frequently reported in children ages 1 – 5 than in children ages 12 – 17 (2.0% vs. 3.9%; PRR: 0.5, 95% CI: 0.4 – 0.7), while these ADRs were relatively more frequently reported in children ages 6 – 11 than in children ages 12 – 17 (6.1% vs. 3.9%; PRR: 1.5, 95% CI: 1.4 – 1.7).

Other ADRs relatively less frequently reported in children ages 1 – 5 and 6 – 11 than in children ages 12 – 17 were related to hepatic disorders (1.0% vs. 2.1%; PRR: 0.5, 95% CI: 0.3 – 0.7 and 1.4% vs. 2.1%; PRR: 0.7, 95% CI: 0.6 – 0.8, respectively) and hematopoietic cytopenias (1.8% vs. 3.8%; PRR: 0.5, 95% CI: 0.4 – 0.6 and 1.9% vs. 3.8%; PRR: 0.5, 95% CI: 0.4 – 0.6, respectively). Another pronounced difference was found in reported ADRs related to breathing abnormalities and respiratory rate, as these were relatively more frequently reported in children ages 1 – 5 than in children ages 12 – 17 (2.5% vs. 1.1%; PRR: 2.4, 95% CI: 1.9–3.0).

ADRs stratified according to reporter type

In total, 11,766 (26.0%) ADRs were reported by consumers and 27,350 (60.5%) by health care professionals (Figure 2). The relative reporting frequencies differed

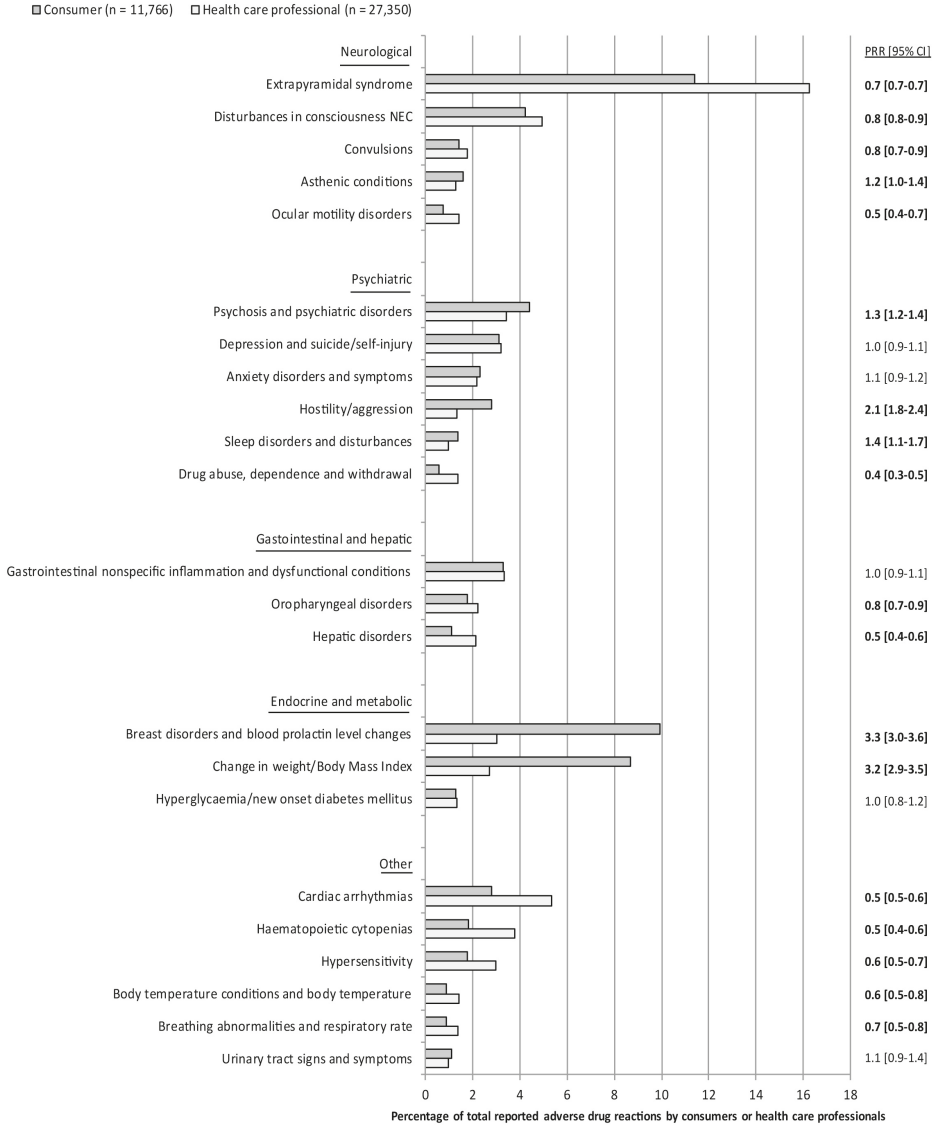
between consumers and health care professionals. ADRs related to hepatic disorders (1.1% vs. 2.1%; PRR: 0.5, 95% CI: 0.4 – 0.6), cardiac arrhythmias (2.8% vs. 5.4%; PRR: 0.5, 95% CI: 0.5 – 0.6), and hematopoietic cytopenias (1.8% vs. 3.8%; PRR: 0.5, 95% CI: 0.4 – 0.6) were relatively less frequently reported by consumers compared with health care professionals, whereas ADRs related to breast disorders or blood prolactin level changes (9.9% vs. 3.0%; PRR: 3.3, 95% CI: 3.0 – 3.6) and change in weight/BMI (8.7% vs. 2.7%; PRR: 3.2, 95% CI: 2.9 – 3.5) were relatively more frequently reported by consumers compared with health care professionals.

DISCUSSION

This study provides an overview of all spontaneously reported ADRs worldwide (1968 – 2017) in children and adolescents treated with an antipsychotic drug. Although the most frequently reported ADRs in children were related to extrapyramidal syndrome, breast disorders or blood prolactin level changes, and cardiac arrhythmias, there were a wide spectrum of reported ADRs. Between males and females, there were few prominent differences in the relative reporting frequencies of ADRs. Differences were more strongly observed between different age classes and between health care professionals and consumers.

The most reported ADRs were in line with previous studies' descriptions of ADRs associated with antipsychotics, including extrapyramidal symptoms, metabolic changes, cardiac arrhythmias, and changes in blood prolactin level.[19–21] Previous studies showed differences between ADRs caused by antipsychotics in males and those in females.[22] Differences were also shown in this study, but these relative differences in reported ADRs in children worldwide were not very prominent. Certain differences in reported ADRs between males and females were expected, as *gynecomastia* was more reported in males and *galactorrhea* more in females. More variability was observed in the relative reporting frequencies between different age classes. A previous study of Sagreiya et al. showed differences in reported ADRs between children, adults, and elderly, whereas this study also shows differences in reported ADRs between younger children and adolescents.[23]

Figure 2. Most reported adverse drug reactions stratified by reporter type and categorized by Standardized Medical Dictionary for Regulatory Activities Queries and clinical reasoning.



Reported adverse drug reactions categorized by SMQs (MedDRA) and clinical reasoning (see Table 1 for details). Reference category: health care professionals. Bold denotes significant difference.
MedDRA, Medical Dictionary for Regulatory Activities; n, number of reported adverse drug reactions; NEC, not elsewhere classified; PRR [95% CI], proportional reporting ratio [95% confidence interval]; SMQs, Standardized MedDRA Queries.

There are various factors that can explain the relative differences in reporting of ADRs between age classes. These differences can be explained by the changes that occur in the human body during a child's development, for instance, in their anatomy and metabolic capacity.[5] Another reason for these differences may be the impact of ADRs on children's everyday lives, as in adolescents, gynecomastia can have a high (emotional) impact on the development of self-esteem and sexual identity.[11] In addition, a fear of needles is greatest in younger children and decreases with age, and therefore, younger children may be less monitored on laboratory parameters due to this fear and some types of ADRs are therefore not noticed.[24] ADRs in younger children are also probably more frequently interpreted and subsequently reported by their parents, while when they grow older they may also identify and report ADRs themselves. The child's perspective can be different than the perspective of the parents or caregivers.[25] Certain ADRs were also expected to be reported less frequently in children ages 1 – 5 than in adolescents, including those related to drug abuse, dependence, and withdrawal.

ADRs were more frequently reported by health care professionals compared with consumers. This is in line with the overall frequency of reporting, irrespective of which drug is used.[26] There were differences between the relative reporting frequency of ADRs reported by health care professionals and those reported by consumers. For example, hepatic disorders and cardiac arrhythmias were relatively more frequently reported by health care professionals, whereas changes in weight/BMI were more frequently reported by consumers. It may be that consumers mostly report those ADRs that influence children's quality of life, that have a high impact on their everyday lives, and are a burden to them, whereas health care professionals might not always count these ADRs as comprising a significant health risk and report more objectively examined ADRs.[27] In addition, health care professionals have access to a laboratory or results of an ECG and consumers do not, whereas the latter can measure the weight of the child and experience emotional changes on a daily basis. Because of these differences, it is important for both health care professionals and consumers to report ADRs.

There are several strengths of using the pharmacovigilance system VigiBase. It is by far the largest ADR database and includes real-life events from clinical practice and not only during a study period, so that also long-term, rare, and nonspecific ADRs can come to light.[14,28] VigiBase is a heterogeneous and worldwide database, with data originating from different sources and types of reporters.[14] In addition, it includes an overall quality-management system.[14]

This study also has some limitations. A pharmacovigilance system is a passive system and includes the risk of underreporting, selective reporting, and missing data, and therefore, there is a risk of reporting bias.[29,30] Data come from a variety

of sources and can be reported incorrectly; no validation of the reported data was performed. Although most reports concerned suspected ADRs, no causality assessment of the evaluated ADR reports was performed nor was the seriousness of the reported ADRs taken into account. In addition, the actual number of children using antipsychotics is unknown; therefore, the use of a pharmacovigilance system implies no quantification of the true risk and no occurrence in absolute terms can be shown.[28] ADRs were categorized by SMQ or clinical reasoning, through which some frequently reported individual ADRs were not included, for example, neuroleptic malignant syndrome and headache. ADRs were not categorized and analyzed by a suspected antipsychotic drug; this was beyond the scope of this study.

CONCLUSIONS

A wide spectrum of ADRs were reported in children treated with antipsychotics. Most prominent differences in relative reporting frequencies were observed between age classes and between health care professionals and consumers, and less prominent between genders. The relative differences in reporting frequency can be of help to tailor information about possible ADRs and to monitor for ADRs. By reporting ADRs by health care professionals, children, and their caregivers, new and rare ADRs can come to light in the short and long term, and the frequency of occurrence can become clearer, which is essential in enlarging the knowledge on safety in the use of antipsychotics in children and making more balanced choices in the therapy.

CLINICAL SIGNIFICANCE

The reported ADRs can be serious and may have a great impact on the daily life of a child, and therefore, it is highly important for health care professionals to give children and their caregivers sufficient information about the ADRs that might occur and to monitor the children for ADRs. To provide sufficient information, it is important for the health care professionals to discuss ADRs with children treated with antipsychotics to become more aware of ADRs that are a burden to the child and may influence compliance to therapy. In addition, the child and the caregivers can write down their experiences on a daily basis, to evaluate changes in effect and the occurrence of ADRs in time. Regarding monitoring, clear instructions are needed. Unfortunately, most instructions on monitoring do not provide sufficient and clear information to be applicable in daily clinical practice and are often not completely followed by the health care professionals.[31,32] Reporting of ADRs by both health care professionals and children or their caregivers is important to gain more knowledge on the occurrence of ADRs in children treated with antipsychotics. To stimulate the

spontaneous reporting of ADRs and reduce underreporting, education, training, and providing reporters with feedback and incentives are essential.[30] Monitoring, reporting, and the awareness of (possible) ADRs by health care professionals, children, and their caregivers could improve the safety of antipsychotic drug use and could help making more balanced choices for antipsychotic drug treatment in children.

Acknowledgements

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Conflict of interest

Els van den Ban received a travel reimbursement from Medice to attend an international scientific convention on child and adolescent psychiatry (2017). The authors declare no conflicts of interest.

Disclaimer

The information in this article does not represent the opinion of the WHO, the UMC, or the national centers.

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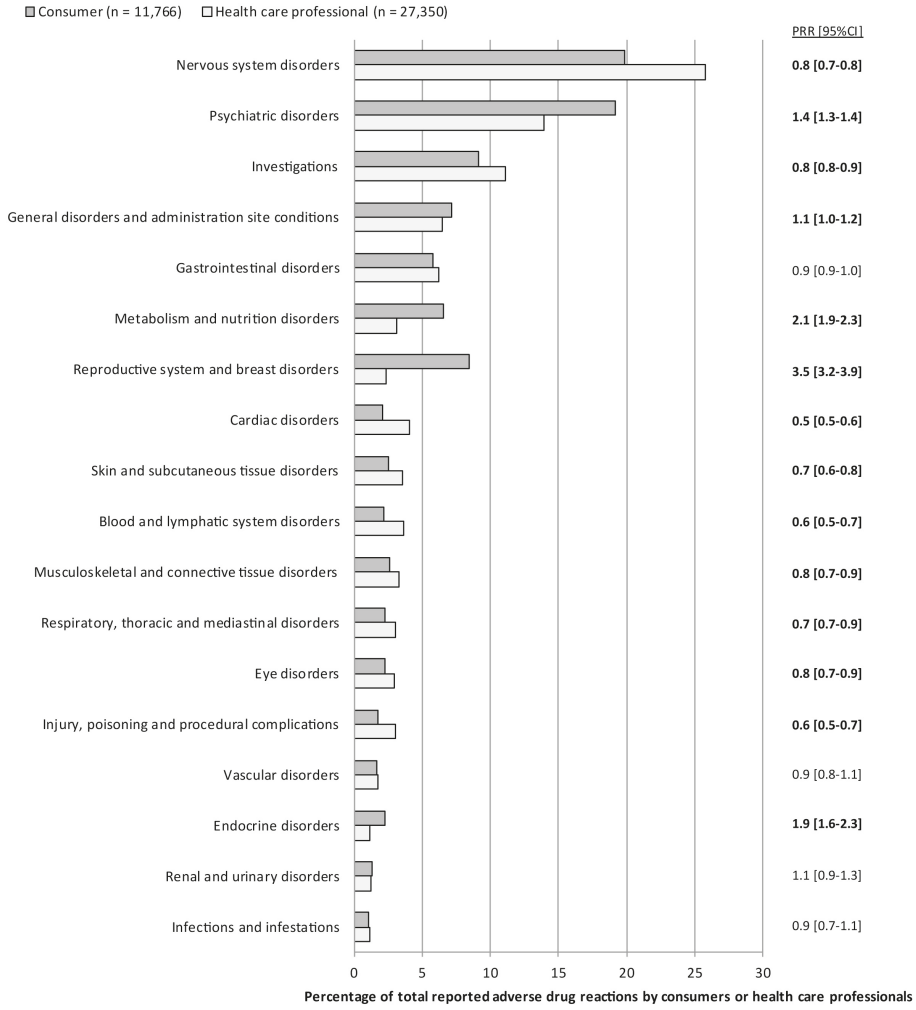
SUPPLEMENTARY MATERIALS

Figure S1. Most reported adverse drug reactions stratified by reporter type, categorized by system organ class.



Reference category: health care professionals. Bold indicates significant difference.
n, number of reported adverse drug reactions; PRR [95% CI], proportional reporting ratio [95% confidence interval].

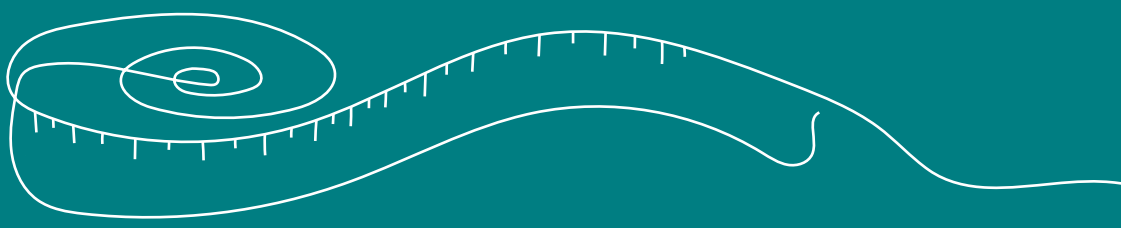
Table S1. Most reported adverse drug reactions categorized by system organ class.

	Total	Gender			Age (years old)				
	n = 45,201	Male n = 27,536	Female n = 16,654	Male/Female	1 – 5 n = 3,232	1-5/12-17	6 – 11 n = 11,296	6-11/12-17	12 – 17 n = 30,673
	%	%	%	PRR [95%CI]	%	PRR [95%CI]	%	PRR [95%CI]	%
Nervous system disorders	23.9	23.5	24.1	1.0 [0.9-1.0]	31.6	**1.4 [1.3-1.5]**	24.7	**1.1 [1.0-1.1]**	22.8
Psychiatric disorders	15.7	15.5	16.0	1.0 [0.9-1.0]	14.0	0.9 [0.9-1.0]	17.9	**1.2 [1.1-1.3]**	15.0
Investigations	10.2	10.5	9.7	**1.1 [1.0-1.1]**	6.1	**0.6 [0.5-0.6]**	9.6	**0.9 [0.8-0.9]**	10.9
General disorders and administration site conditions	6.8	6.9	6.9	1.0 [0.9-1.1]	8.9	**1.4 [1.2-1.5]**	7.0	1.1 [1.0-1.2]	6.5
Gastrointestinal disorders	6.1	5.9	6.4	0.9 [0.9-1.0]	5.7	0.9 [0.8-1.1]	6.2	1.0 [0.9-1.1]	6.1
Metabolism and nutrition disorders	4.5	5.1	3.7	**1.4 [1.3-1.5]**	3.6	0.8 [0.7-1.0]	5.7	**1.3 [1.2-1.5]**	4.2
Reproductive system and breast disorders	4.0	4.3	3.6	**1.2 [1.1-1.3]**	1.5	**0.4 [0.3-0.5]**	4.0	0.9 [0.9-1.1]	4.2
Cardiac disorders	3.5	3.5	3.6	1.0 [0.9-1.1]	3.7	0.9 [0.8-1.1]	2.5	**0.6 [0.6-0.7]**	3.9
Skin and subcutaneous tissue disorders	3.2	3.2	3.3	0.9 [0.9-1.0]	2.6	0.8 [0.7-1.0]	3.6	**1.1 [1.0-1.3]**	3.1
Blood and lymphatic system disorders	3.1	3.2	3.0	1.1 [1.0-1.2]	2.0	**0.5 [0.4-0.7]**	1.7	**0.4 [0.4-0.5]**	3.8

Table S1. Continued

	Total	Gender			Age (years old)				
	n = 45,201	Male n = 27,536	Female n = 16,654	Male/Female	1 – 5 n = 3,232	1-5/12-17	6 – 11 n = 11,296	6-11/12-17	12 – 17 n = 30,673
	%	%	%	PRR [95%CI]	%	PRR [95%CI]	%	PRR [95%CI]	%
Musculoskeletal and connective tissue disorders	3.1	3.2	2.7	**1.2 [1.1-1.3]**	2.8	0.9 [0.7-1.1]	3.0	1.0 [0.9-1.1]	3.1
Respiratory, thoracic and mediastinal disorders	2.8	2.8	2.7	1.1 [0.9-1.2]	4.7	**1.8 [1.5-2.2]**	2.8	1.1 [0.9-1.2]	2.6
Eye disorders	2.7	2.6	2.9	**0.9 [0.8-1.0]**	2.8	1.0 [0.8-1.3]	2.8	1.1 [0.9-1.2]	2.7
Injury, poisoning and procedural complications	2.6	2.1	3.1	**0.7 [0.6-0.8]**	2.8	1.0 [0.8-1.2]	1.7	**0.6 [0.5-0.7]**	2.9
Vascular disorders	1.7	1.6	2.0	**0.8 [0.7-0.9]**	1.5	0.8 [0.6-1.0]	1.2	**0.6 [0.5-0.7]**	2.0
Endocrine disorders	1.4	1.4	1.5	0.9 [0.8-1.1]	0.4	**0.3 [0.2-0.5]**	1.6	1.1 [0.9-1.3]	1.5
Renal and urinary disorders	1.3	1.4	1.1	**1.2 [1.0-1.5]**	1.0	0.8 [0.5-1.1]	1.3	1.0 [0.8-1.2]	1.3
Infections and infestations	1.2	1.1	1.3	0.9 [0.7-1.0]	1.2	1.0 [0.7-1.3]	1.0	0.8 [0.7-1.0]	1.2

System organ classes including >1% of total reported adverse drug reactions. Bold values indicate significant difference.
n, number of reported adverse drug reactions; PRR [95%CI], proportional reporting ratio [95% confidence interval].



Chapter 3

Monitoring in daily clinical practice

Chapter 3.1

Monitoring of metabolic, cardiac, and endocrine indicators in youth treated with antipsychotics as reported by health care professionals

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J Clin Psychopharmacol. 2018;38(5):489–493.

ABSTRACT

Objective

It is unclear how youth treated with antipsychotics are monitored. The purpose of this study was to assess monitoring of metabolic, cardiac, and endocrine indicators in youth (<18 years old) treated with antipsychotics as reported by health care professionals in the Netherlands.

Methods

A questionnaire was designed to collect information from health care professionals regarding the monitoring of youth treated with antipsychotics. Data were collected at a national conference.

Results

Fifty-nine health care professionals completed the questionnaire, of which 53 (89.8%) were child and adolescent psychiatrists (approximately 20% of all child and adolescent psychiatrists in the Netherlands). More than 80% of respondents reported monitoring physical indicators — weight, height, body mass index, heart rate, and blood pressure — and over 50% reported monitoring laboratory indicators — lipid profile, blood glucose, and prolactin level. Most of the respondents reported monitoring physical indicators more than twice per year and laboratory indicators once per year. Almost all respondents (56/59, 94.9%) reported monitoring according to a clinical guideline or protocol. Only 1 respondent reported monitoring the indicators completely according to the clinical guideline. Respondents mentioned that facilitating factors for monitoring, such as access to electrocardiogram facilities, were insufficiently available.

Conclusion

Although all health care professionals reported monitoring metabolic, cardiac, and endocrine indicators in youth treated with antipsychotics, great variability exists in reported monitoring practices. Factors contributing to this variability must be assessed to optimize the benefit-risk ratio for the individual patient.

INTRODUCTION

Antipsychotics are frequently prescribed to youth to treat psychiatric disorders, including attention-deficit/hyperactivity disorder, autism spectrum disorder, and disruptive behavior disorders.[1,2] Individual antipsychotics have received marketing authorization for some of these indications, but off-label prescribing is common.[3,4] Frequent and off-label use of antipsychotics in youth is concerning because of the risks of serious adverse effects and limited evidence regarding the (long-term) benefit-risk ratio.

Antipsychotics have been associated with clinically relevant endocrine and cardiometabolic adverse effects, including weight gain, dyslipidemia, development of type 2 diabetes mellitus, hyperprolactinemia, and prolonged QT interval.[5–8] These may occur in both adults and youth, but less is known about adverse effects in youth, and younger age is an established risk factor for greater weight gain with atypical antipsychotics.[9]

Pharmacotherapy with antipsychotics should consist of not only prescribing but also monitoring for efficacy and adverse effects to periodically evaluate the benefit-risk ratio in individual patients and adjust pharmacotherapy when necessary. Several clinical guidelines worldwide describe how to monitor for adverse effects of antipsychotics in youth. However, these guidelines differ not only in which indicators to monitor and the frequency of monitoring but also in treatment options when the outcome deviates from the baseline or reference value. For example, some guidelines recommend continual monitoring of the lipid profile,[10–12] whereas other guidelines recommend monitoring the lipid profile only when risk factors, such as a high body mass index (BMI), are present[13] or depending on the type of antipsychotic used.[14]

Considering this variability in monitoring guidelines, the purpose of this study was to assess monitoring of metabolic, cardiac, and endocrine indicators in youth (<18 years old) treated with antipsychotics as reported by health care professionals in the Netherlands.

MATERIALS AND METHODS

Questionnaire design

A questionnaire was designed to collect information related to current clinical practices regarding monitoring of metabolic, cardiac, and endocrine indicators in youth treated with antipsychotics. The questionnaire was pretested and reviewed by 4 child and adolescent psychiatrists from an outpatient clinic in Utrecht who have experience in prescribing antipsychotics, as well as 6 colleagues of the division of Pharmacoepidemiology and Clinical Pharmacology of Utrecht University.

The final questionnaire included 15 questions concerning monitoring, based on current clinical guidelines and the items used for the Systematic Information for Monitoring score.[10,12–16] Most questions were multiple choice, with the option to include additional comments. The questions concerned 1) reasons to start and stop monitoring; 2) which metabolic, cardiac, and endocrine indicators were monitored; 3) time frames of treatment in which these indicators were monitored; 4) frequency of monitoring; 5) response to monitoring results; 6) whether a clinical guideline or protocol was followed and which clinical guideline or protocol was followed; and 7) whether facilitating factors or barriers for monitoring were present. The indicators included in the questionnaire were lipid profile, blood glucose, prolactin, antipsychotic drug level, weight, height, BMI, fat mass or fat percentage, waist and hip circumference, heart rate, blood pressure, and QTc interval or electrocardiogram (ECG). Three time frames for monitoring were specified: at start of antipsychotic treatment, during the first 3 months of treatment, and after 3 months of treatment. The frequency of monitoring at start and during the first 3 months of treatment was defined as "never," "sometimes, in case of …," and "always/almost always," and the frequency after 3 months as "never," "less than once per year," "once per year," "twice per year," "more than twice per year," and "other, namely: … ." Facilitating factors for monitoring included access to a laboratory, tape measure, scale, and the ability to obtain an ECG. The full questionnaire can be found in Supplementary Item 1 (Dutch), Supplemental Digital Content 1, http://links.lww.com/JCP/ A526 and Supplementary Item 2 (English), Supplemental Digital Content 2, http://links.lww.com/JCP/A527.

The institutional review board of the Department of Pharmaceutical Sciences of Utrecht University approved the study. A review by the ethics committee was not required because the data collected were anonymous and included no information on individuals; no patient data were used.

Setting, study population, and data collection

Data were collected at the national conference *Van Wijk tot Wetenschap* for child and adolescent psychiatry in Utrecht, the Netherlands, in November 2016. All prescribers present at the conference were invited by trained undergraduate students of Utrecht University to complete the questionnaire during the conference. Prescribers did not receive incentives to participate. The questionnaire required approximately 10 minutes to complete.

Analysis

Data entry and review were conducted by the first author (L.M.). Discrepancies and indistinct answers were discussed and resolved by consensus with 2 additional reviewers (E.H., T.E.). Descriptive statistics were performed using SPSS Statistics version 24.

RESULTS

Fifty-nine health care professionals completed the questionnaire (Table 1); this number amounts to 46% of the physicians and clinical nurse specialists present at the conference. Fifty-three (89.8%) respondents were child and adolescent psychiatrists; this is approximately 20% of the total number of practicing child and adolescent psychiatrists in the Netherlands.

The respondents reported that the main reasons to start monitoring metabolic, cardiac, and endocrine indicators were early detection of changes in physical or laboratory indicators (48/59, 81.4%), presence of risk factors including diabetes mellitus before start of antipsychotic treatment (44/59, 74.6%), and recommendation by a guideline (42/59, 71.2%). The main reasons reported to stop monitoring were end of antipsychotic therapy (39/59, 66.1%) and youth not willing to provide a blood sample anymore (21/59, 35.6%).

Table 1. Characteristics of the study population (n = 59)

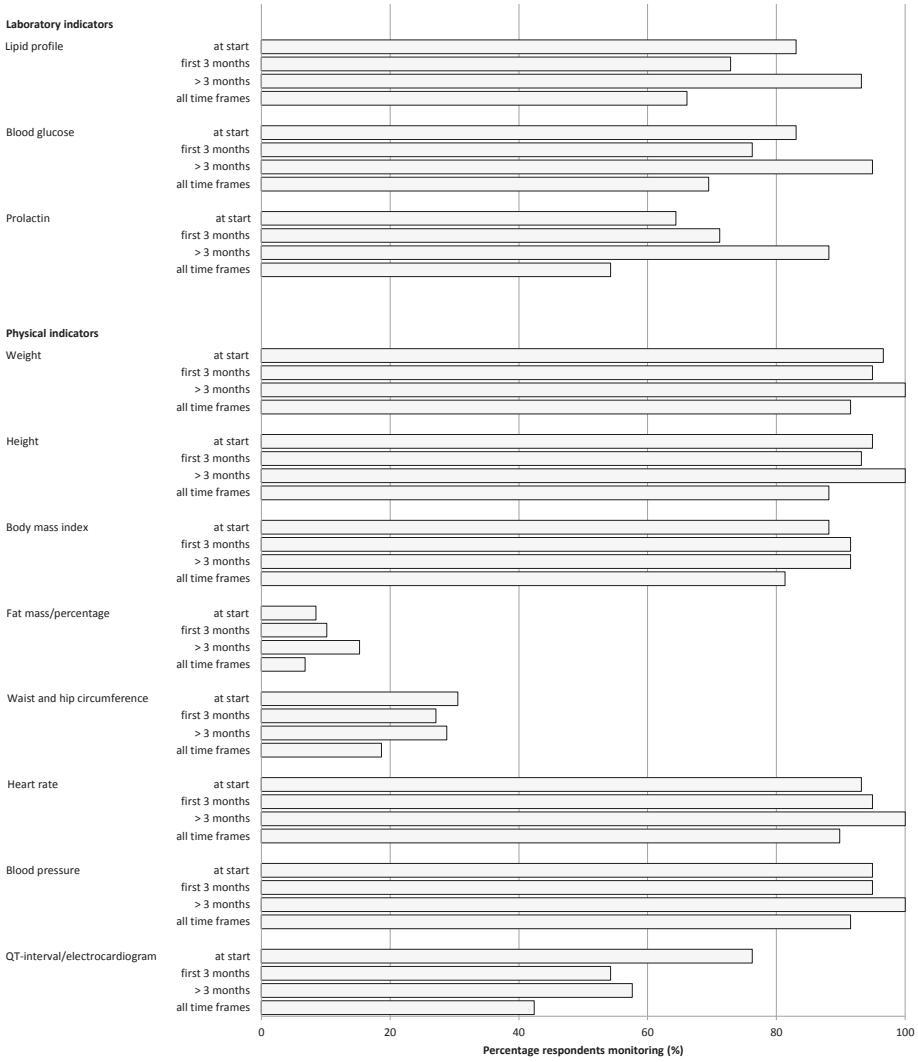
Characteristic	n	(%)
Specialism		
Child and adolescent psychiatrist	53	(89.8)
Pediatrician	3	(5.1)
General practitioner	2	(3.4)
Clinical nurse specialist	1	(1.7)
Health care setting *		
Mental health services, youth	48	(81.4)
(Academic) Hospital	7	(11.9)
Private practice	6	(10.2)
Mental health services, general	5	(8.5)
Other	4	(6.8)
Years prescribing		
0-1	0	(0.0)
2-5	9	(15.3)
6-10	13	(22.0)
>10	37	(62.7)
Number of youth prescribed antipsychotics to (last 6 months)		
<10	21	(35.6)
10-20	15	(25.4)
>20	23	(39.0)
Use of a guideline		
Yes	56	(94.9)
No	3	(5.1)

* Ten respondents worked in more than one health care setting; therefore, total n >59 (>100%).

More than 80% of respondents reported monitoring (sometimes or always) the physical indicators weight, height, BMI, heart rate, and blood pressure when antipsychotic treatment was started in youth, during the first 3 months of treatment and after 3 months (Figure 1). More than half of respondents reported monitoring the laboratory indicators lipid profile, blood glucose, and prolactin level when antipsychotic treatment was started in youth, during the first 3 months of treatment, and after 3 months. Indicators least frequently monitored were fat mass or fat percentage and waist and hip circumference. Not a single respondent reported monitoring all laboratory and physical indicators (Figure 1) when starting antipsychotic treatment in youth, during the first 3 months of treatment, and after 3 months. When monitoring of fat mass or fat percentage was excluded, 3.4% (2/59) of respondents reported monitoring all remaining laboratory and physical indicators in

all 3 time frames. When monitoring of fat mass or fat percentage and monitoring of waist and hip circumference were excluded, 20.3% (12/59) of respondents reported monitoring all remaining laboratory and physical indicators in all 3 time frames.

Figure 1. Monitoring of metabolic, cardiac, and endocrine indicators in youth treated with antipsychotics as reported by health care professionals (n = 59).



Most respondents reported monitoring laboratory indicators once per year when treatment with antipsychotics lasted longer than 3 months; lipid profile was monitored once per year by 55.9% (33/59) of respondents, blood glucose by 57.6% (34/59), and prolactin level by 40.7% (24/59). The physical indicators weight, height,

BMI, heart rate, and blood pressure were reported to be monitored more frequently by the majority of respondents (more than twice per year); weight and height were each monitored more than twice per year by 44.1% (26/59) of respondents, BMI by 40.7% (24/59), heart rate by 35.6% (21/59), and blood pressure by 37.3% (22/59). The majority of respondents who reported monitoring the QTc interval or ECG indicated that they monitored this indicator only when risk factors were present.

In total, 16 (27.1%) respondents reported that they have not changed therapy because of monitoring results within the last 6 months, 38 (64.4%) respondents reported that they have changed therapy for less than 25% of the youth for whom they had prescribed antipsychotics, and 5 (8.5%) respondents have changed therapy for 25% to 50% of the youth for whom they had prescribed antipsychotics.

In total, 94.9% (56/59) of respondents reported monitoring according to a guideline or protocol. Most of the respondents followed a Dutch guideline (39/59, 66.1%), an international guideline (4/59, 6.8%), or both (4/59, 6.8%).[10,13] Only 1 of these respondents reported monitoring lipid profile, blood glucose, prolactin level, weight, height and BMI throughout the entire course of treatment according to the guideline followed. More than half of the respondents who claimed to follow a Dutch guideline reported always monitoring lipid profile (23/43, 53.5%) and blood glucose (25/43, 58.1%) when treatment with antipsychotics was started, although the guideline advises monitoring these indicators only when risk factors are present.[13]

Not all respondents reported that factors to facilitate monitoring were sufficiently available. In total, 98.3% (58/59) of respondents reported that a scale was available, 91.5% (54/59) a tape measure, 94.9% (56/59) a blood pressure monitor, 83.1% (49/59) access to outcomes of laboratory indicators, 81.4% (48/59) access to a laboratory, 74.6% (44/59) ability to consult another specialist, 49.2% (29/59) access to facilities to obtain an ECG, and 49.2% (29/59) potential for referral if the child has a fear of needles.

DISCUSSION

Although all health care professionals who completed the questionnaire reported monitoring metabolic, cardiac, and endocrine indicators in youth treated with antipsychotics, there was great variability in monitoring between these respondents. This involved not only which laboratory and physical indicators were monitored in the 3 time frames but also the frequency of monitoring. Although most of the respondents reported monitoring according to a guideline, almost none reported actually monitoring all laboratory and physical indicators according to the guideline they claimed to follow.[10,13]

To optimize monitoring, it is important to know the cause of the variability. First, guidelines differ in type, frequency, and method of monitoring metabolic, cardiac, and endocrine indicators. For example, the National Institute for Health and Clinical Excellence guideline and the guideline of the American Academy of Child and Adolescent Psychiatry offer advice regarding when an ECG should be considered, but neither the guideline of the Canadian Alliance for Monitoring Effectiveness and Safety of Antipsychotics in Children nor the Dutch guideline advises when to monitor for changes in the ECG.[10,12–14] Furthermore, previous studies have shown that instructions in guidelines regarding monitoring are often incomplete or do not provide sufficient information to be applicable in daily clinical practice.[17,18] Consequently, physicians may interpret the instructions differently and as a result monitor youth treated with antipsychotics differently. Therefore, guidelines must be uniform, informative, comprehensible, and passably simple for everyday practice.

Second, respondents of this study reported that facilitating factors for monitoring were not always sufficiently available. Similarly, in a previous study, health care professionals reported inadequate access to factors that facilitate monitoring, such as a tape measure, blood pressure monitor, or laboratory facilities.[19] This lack of facilitating factors should be resolved to adequately monitor youth in daily clinical practice.

Finally, only 1 of the respondents of this study reported complying with the guideline that was claimed to be followed. Lack of adherence by health care professionals to monitoring guidelines has been reported before and may have several reasons, including lack of reminder systems, lack of time, insufficient knowledge about monitoring, or attitudes concerning monitoring.[20–23] Furthermore, the attitude of the youth and parents regarding monitoring is essential as well. Youth may resist monitoring because of fear of needles, and parents may feel resistant when their child does not desire to be monitored or when they do not have ample knowledge concerning the need for monitoring.[21]

Treatment of youth with antipsychotics is more than just prescribing medication; it should also involve adequate monitoring for efficacy, adverse effects, and safety, as well as adjustment of therapy when necessary. It is important to be aware of the different factors that can result in variability in monitoring, because only then can these factors be discussed, possibly resolved, and variability minimized. Following this approach, individual children can be offered the same treatment, including adequate monitoring of metabolic, cardiac, and endocrine indicators.

However, this study shows that not every physician agrees upon adequate methods of monitoring. Several respondents indicated that they would like a clear national guideline concerning the manner and frequency of monitoring metabolic,

cardiac, and endocrine indicators in youth treated with antipsychotics. In such a guideline, a balance must be found between the benefit and the burden for a child treated with antipsychotics. Not only are knowing which indicators to monitor and the frequency of monitoring significant considerations, but also all health care professionals involved must understand appropriate interventions when the outcome deviates from the baseline or reference value and suitable treatments for somatic consequences of antipsychotics.[19] For this to occur, cooperation between child and adolescent psychiatrists, nurse practitioners, general practitioners, and pediatricians is necessary. Furthermore, electronic medical records could provide reminders when monitoring is due and thus improve adherence to clinical guidelines.

Strengths and limitations

A strength of this study is that the prescribers included worked in various health care settings throughout the Netherlands. Most were experienced prescribers with greater than 10 years of prescribing antipsychotics. They completed the questionnaire on the spot; therefore, it was not likely that they searched for information elsewhere but reported on actual daily clinical practice.

A limitation of this study is the relatively small number of prescribers who completed the questionnaire and whether these prescribers were representative of all prescribers of antipsychotics to youth in the Netherlands. Although the number is low, approximately 20% of all child and adolescent psychiatrists in the Netherlands completed the questionnaire. Other physicians, including general practitioners and pediatricians, were underrepresented. Social or professional desirability response bias may have led to overreporting of monitoring in youth treated with antipsychotics. In addition, physicians who attended this conference may be more aware and motivated to follow current guidelines, which could also lead to bias.

CONCLUSION

Treatment with antipsychotics includes frequent monitoring for efficacy and adverse effects. Although all health care professionals reported monitoring metabolic, cardiac, and endocrine indicators in youth treated with antipsychotics, there was great variability in which indicators were monitored and the frequency of monitoring. Almost none of the respondents who reported monitoring according to a guideline did follow this guideline completely. Factors contributing to variability, including the availability of facilitating factors and the reasons whether to start or stop monitoring, must be assessed to optimize monitoring practices and the benefit-risk ratio of antipsychotics for the individual patient.

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Conflict of interest

Els van den Ban received a travel reimbursement to an international scientific child and adolescent psychiatry convention by Medice. The authors declare no conflicts of interest.

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SUPPLEMENTARY MATERIALS

Item 1. Questionnaire Dutch

Monitoren van kinderen en adolescenten die antipsychotica gebruiken

Achtergrondinformatie:
Gebruik van een antipsychoticum brengt naast gewenste effecten ook bijwerkingen met zich mee. In Nederland is er geen nationale richtlijn die de werkwijze beschrijft rondom het monitoren van kinderen en adolescenten die een antipsychoticum gebruiken. Wel zijn er lokale richtlijnen en worden er adviezen uitgebracht. Het is echter niet duidelijk wat er in de praktijk daadwerkelijk gedaan wordt.

Met behulp van deze korte vragenlijst willen wij in kaart brengen wat er in de dagelijkse praktijk gebeurt op het gebied van het monitoren van kinderen en adolescenten die een antipsychoticum gebruiken. Deze vragenlijst richt zich op het klinisch monitoren op metabole, endocriene en cardiale bijwerkingen door middel van laboratorium- of lichamelijk onderzoek. Tevens willen we op deze manier samen met u kijken waar mogelijk nog verbetering gewenst is om het monitoren op deze bijwerkingen zo goed mogelijk vorm te geven.

- **Doel:** in kaart brengen wat er in de dagelijkse praktijk gebeurt op het gebied van het monitoren op metabole, endocriene en cardiale bijwerkingen door middel van laboratorium- of lichamelijk onderzoek bij kinderen en adolescenten (< 18 jaar) die een antipsychoticum gebruiken.
- **Doelgroep:** voorschrijvers van antipsychotica aan kinderen en adolescenten.
- **Tijdsduur:** 5-10 minuten
- De vragenlijst vult u **anoniem** in.

Universiteit Utrecht
Utrecht Institute for Pharmaceutical Sciences (UIPS)
Afdeling Farmaco-epidemiologie en Klinische Farmacologie

Datum: 24 november 2016

Onderzoekers:
Prof. dr. A.C.G. Egberts, hoogleraar Klinische farmacie
Dr. E.R. Heerdink, universitair hoofddocent
Dr. E.F. van den Ban, kinder- en jeugdpsychiater
L. Minjon MSc., apotheker/promovendus

1. Wat monitort u bij kinderen en adolescenten die voor de eerste keer een antipsychoticum voorgeschreven krijgen?

Geef in de tabel aan hoe vaak u de genoemde waarden meet bij de start met een antipsychoticum.
Indien u een waarde 'soms' meet, geef aan in welke situaties dit is.

		Frequentie	
Onderzoek	Nooit	Soms, indien…	Altijd/ vrijwel altijd
Laboratorium			
Lipidenspectrum *Totaal cholesterol, HDL, LDL, TG*	○	○_____	○
Bloedglucose *Glucose, HbA1c*	○	○_____	○
Prolactine	○	○_____	○
Spiegel antipsychoticum	○	○_____	○
Lichamelijk			
Gewicht	○	○_____	○
Lengte	○	○_____	○
BMI	○	○_____	○
Vetmassa / vetpercentage	○	○_____	○
Taille- en heupomvang	○	○_____	○
Hartslag	○	○_____	○
Bloeddruk	○	○_____	○
QT-interval / ECG	○	○_____	○
Anders			
_____	○	○_____	○
_____	○	○_____	○

2. Wat monitort u bij kinderen en adolescenten <u>gedurende de eerste drie maanden</u> dat zij een antipsychoticum gebruiken?

Geef in de tabel aan hoe vaak u de genoemde waarden meet gedurende de eerste drie maanden na de start met een antipsychoticum.
Indien u een waarde 'soms' meet, geef aan in welke situaties dit is.

		Frequentie	
Onderzoek	Nooit	Soms, indien…	Altijd/ vrijwel altijd
Laboratorium			
Lipidenspectrum *Totaal cholesterol, HDL, LDL, TG*	○	○ _____	○
Bloedglucose *Glucose, HbA1c*	○	○ _____	○
Prolactine	○	○ _____	○
Spiegel antipsychoticum	○	○ _____	○
Lichamelijk			
Gewicht	○	○ _____	○
Lengte	○	○ _____	○
BMI	○	○ _____	○
Vetmassa / vetpercentage	○	○ _____	○
Taille- en heupomvang	○	○ _____	○
Hartslag	○	○ _____	○
Bloeddruk	○	○ _____	○
QT-interval / ECG	○	○ _____	○
Anders			
_____	○	○ _____	○
_____	○	○ _____	○

3. Wat monitort u bij een kind of adolescent die een antipsychoticum gebruikt gedurende een periode <u>langer dan drie maanden</u>?

Geef in de tabel aan hoe vaak u de genoemde waarden doorgaans meet.
Indien u een waarde 'anders' meet, geef dan naast de andere frequentie ook aan in welke situaties dit is.

	Frequentie					
Onderzoek	Nooit	< 1x per jaar	1x per jaar	2x per jaar	> 2x per jaar	Anders, namelijk...
Laboratorium						
Lipidenspectrum *Totaal cholesterol, HDL, LDL, TG*	○	○	○	○	○	○_____
Bloedglucose *Glucose, HbA1c*	○	○	○	○	○	○ _____
Prolactine	○	○	○	○	○	○ _____
Spiegel antipsychoticum	○	○	○	○	○	○ _____
Lichamelijk						
Gewicht	○	○	○	○	○	○ _____
Lengte	○	○	○	○	○	○ _____
BMI	○	○	○	○	○	○_____
Vetmassa / vetpercentage	○	○	○	○	○	○_____
Taille- en heupomvang	○	○	○	○	○	○ _____
Hartslag	○	○	○	○	○	○ _____
Bloeddruk	○	○	○	○	○	○ _____
QT-interval / ECG	○	○	○	○	○	○ _____
Anders						
_____	○	○	○	○	○	○ _____
_____	○	○	○	○	○	○ _____

De volgende vragen richten zich op het klinisch monitoren van kinderen en adolescenten op de bepalingen aangegeven bij vraag 1-3.

4. Aan hoeveel kinderen en adolescenten heeft u in totaal de afgelopen zes maanden een antipsychoticum voorgeschreven?

Dit betreft alle kinderen en adolescenten die een eerste recept of een herhaalrecept hebben gekregen.
Geef een schatting van het totale aantal.

□ < 10
□ 10-20
□ > 20

5. Waarom start u met het monitoren van kinderen en adolescenten die een antipsychoticum (gaan) gebruiken?

Meerdere antwoorden mogelijk.

□ Niet van toepassing, ik monitor nooit.
□ Om een keuze te kunnen maken voor een bepaald antipsychoticum.
□ Om de dosering van het antipsychoticum in te stellen.
□ Om afwijkingen in uitslagen van laboratorium- of lichamelijk onderzoek tijdig te signaleren.
□ Er zijn voor de start al risicofactoren aanwezig, zoals diabetes mellitus, een hoog BMI of familiaire hypercholesterolemie.
□ Dit is volgens de door mij gebruikte richtlijn.
□ Anders, namelijk.....

6. Waarom <u>start u niet met het monitoren</u> van kinderen en adolescenten die een antipsychoticum (gaan) gebruiken?

Meerdere antwoorden mogelijk.

- ☐ Niet van toepassing, ik monitor altijd.
- ☐ Het kind/de adolescent wil niet geprikt worden (prikangst).
- ☐ Het monitoren is te belastend voor het kind/de adolescent.
- ☐ De ouders/verzorgers willen niet dat er gemonitord wordt.
- ☐ Vanwege de kans dat de therapietrouw omlaag gaat als het kind/de adolescent of de ouders/verzorgers zich meer bewust is/zijn van de bijwerkingen.
- ☐ Het monitoren zoals beschreven in de door mij gebruikte richtlijn vind ik onnodig.
- ☐ De faciliteiten om te monitoren zijn niet toereikend.
- ☐ Anders, namelijk.....

7. Waarom <u>stopt u met het monitoren</u> van kinderen en adolescenten die een antipsychoticum gebruiken?

Meerdere antwoorden mogelijk.

- ☐ De gemeten waarden liggen binnen de door mij gebruikte referentiewaarden.
- ☐ De gemeten waarden zijn stabiel.
- ☐ Er zijn geen symptomen van bijwerkingen.
- ☐ Het kind/de adolescent is goed ingesteld qua effectiviteit.
- ☐ De patiënt is volwassen (≥ 18 jaar).
- ☐ Het antipsychoticum wordt gestaakt.
- ☐ Het kind/de adolescent wil niet (meer) geprikt worden.
- ☐ Anders, namelijk.....

8. In welke mate wordt de uitvoering van het monitoren gefaciliteerd op de werkvloer?

Geef in de tabel aan wat u voldoende of onvoldoende tot uw beschikking heeft.

	Voldoende	Onvoldoende
Weegschaal	○	○
Meetlint / meetlat	○	○
Bloeddrukmeter	○	○
Laboratorium	○	○
Inzicht in laboratoriumuitslagen	○	○
Faciliteiten voor het maken van een ECG	○	○
Vragenlijsten over bijwerkingen	○	○
Toegankelijk overleg met een ander specialisme	○	○
Mogelijkheden voor doorverwijzing i.v.m. prikangst	○	○
Anders, namelijk:	○	○

9. Bij welk percentage van de kinderen en adolescenten die u de afgelopen zes maanden een antipsychoticum heeft voorgeschreven, heeft een wijziging plaatsgevonden in de therapie naar aanleiding van de uitslag van het monitoren?

Dit betreft alle wijzigingen, zowel medicamenteus als niet medicamenteus.
Geef een schatting van het percentage.

□ Dit is niet voorgekomen
□ < 25%
□ 25-50%
□ 50-75%
□ > 75%

10. Indien er een wijziging in de therapie plaatsvindt naar aanleiding van de uitslag van het monitoren, om wat voor <u>type wijziging</u> gaat dit dan?

Geef in de tabel aan hoe vaak een type wijziging plaatsvindt.

	Frequentie				
Wijziging	Nooit	Zelden	Soms	Meestal	Altijd
Doseringswijziging antipsychoticum	○	○	○	○	○
Switchen antipsychoticum	○	○	○	○	○
Staken antipsychoticum (geen switch)	○	○	○	○	○
Wijziging in de overige farmacotherapie	○	○	○	○	○
Verwijzing naar een andere specialist	○	○	○	○	○
Andere adviezen, niet medicamenteus *Bijvoorbeeld dieet of lichaamsbeweging*	○	○	○	○	○

11. Maakt u gebruik van een richtlijn waarin het beleid rondom het monitoren op bijwerkingen van antipsychotica bij kinderen en adolescenten beschreven staat?

□ Nee
□ Ja, namelijk:
  □ Formularium Psychofarmaca Accare, Monitoring op metabole en endocriene bijwerkingen van antipsychotica (o.a. beschikbaar via Kenniscentrum Kinder- en Jeugdpsychiatrie)
  □ National Institute for Health and Care Excellence (NICE) guidelines
  □ Een lokaal protocol, namelijk: .....
  □ Anders: .....

12. Wat kan er volgens u nog verbeterd worden omtrent het monitoren van kinderen en adolescenten die een antipsychoticum gebruiken?

Achtergrondinformatie

13. Hoe lang schrijft u al antipsychotica voor aan kinderen en adolescenten?

□ 0-1 jaar
□ 2-5 jaar
□ 6-10 jaar
□ > 10 jaar

14. Wat is uw specialisme en in welke sector bent u op dit moment werkzaam?

Specialisme:

□ Kinder- en jeugdpsychiater
□ Kinderarts
□ Huisarts
□ ANIOS
□ Verpleegkundig specialist
□ Anders, namelijk.....
□ Kinder- en jeugdpsychiater i.o.
□ Kinderarts i.o.
□ Huisarts i.o.

Sector:
Meerdere antwoorden mogelijk

□ Algemeen ziekenhuis
□ Vrijgevestigde praktijk
□ GGZ-instelling, kind en jeugd
□ GGZ-instelling, algemeen
□ Instelling voor mensen met een verstandelijke beperking
□ Anders, namelijk.....

15. Eventuele opmerkingen

Bedankt voor uw medewerking!

Item 2. Questionnaire English

Monitoring in youth treated with antipsychotics

Translated from Dutch

Background:
Use of antipsychotics can lead to the development of adverse effects. The Netherlands has no official national guideline regarding the manner in which monitoring for adverse effects in youth treated with antipsychotics should be performed, but there are local guidelines and recommendations. Therefore, it is unclear how monitoring is performed in daily clinical practice.

With this questionnaire, we would like to collect information from health care professionals concerning the monitoring of metabolic, cardiac and endocrine indicators in youth treated with antipsychotics in current clinical practice. We also would like to know whether improvement in monitoring is needed, in your opinion, as well as the requirements to accomplish this improvement.

- **Objective:** to assess monitoring of metabolic, cardiac and endocrine indicators in youth (< 18 years old) treated with antipsychotics as reported by health care professionals.
- **Study population:** prescribers of antipsychotics to youth.
- **Duration:** 5-10 minutes.
- This questionnaire is **anonymous**.

Utrecht University
Utrecht Institute for Pharmaceutical Sciences (UIPS)
Division of Pharmacoepidemiology and Clinical Pharmacology

Date: November 24, 2016

Investigators:
Toine C.G. Egberts PhD, professor Clinical pharmacy
Eibert R. Heerdink PhD, associate professor
Els van den Ban MD PhD, child and adolescent psychiatrist
Lenneke Minjon PharmD, pharmacist/PhD student

1. Which indicators do you monitor <u>at the start</u> in youth treated with antipsychotic medication for the first time?

Indicate in the table the frequency with which you measure the indicators mentioned at the start of antipsychotic treatment.
If you measure an indicator "sometimes," specify the situations in which this occurs.

	Frequency		
Investigation	Never	Sometimes, in case of ...	Always/ almost always
Laboratory indicators			
Lipid profile *Total cholesterol, HDL, LDL, TG*	○	○_____	○
Blood glucose *Glucose, HbA1c*	○	○_____	○
Prolactin	○	○_____	○
Antipsychotic blood level	○	○_____	○
Physical indicators			
Weight	○	○_____	○
Height	○	○_____	○
BMI	○	○_____	○
Fat mass / fat percentage	○	○_____	○
Waist and hip circumference	○	○_____	○
Heart rate	○	○_____	○
Blood pressure	○	○_____	○
QT interval / ECG	○	○_____	○
Other			
_____	○	○_____	○
_____	○	○_____	○

2. Which indicators do you monitor in youth treated with antipsychotic medication during the <u>first three months</u>?

Indicate in the table the frequency with which you measure the indicators mentioned during the first three months after starting antipsychotic treatment.
If you measure an indicator "sometimes," specify the situations in which this occurs.

		Frequency	
Investigation	Never	Sometimes, in case of …	Always/ almost always
Laboratory indicators			
Lipid profile *Total cholesterol, HDL, LDL, TG*	○	○_____	○
Blood glucose *Glucose, HbA1c*	○	○_____	○
Prolactin	○	○_____	○
Antipsychotic blood level	○	○_____	○
Physical indicators			
Weight	○	○_____	○
Height	○	○_____	○
BMI	○	○_____	○
Fat mass / fat percentage	○	○_____	○
Waist and hip circumference	○	○_____	○
Heart rate	○	○_____	○
Blood pressure	○	○_____	○
QT interval / ECG	○	○_____	○
Other			
_____	○	○_____	○
_____	○	○_____	○

3. Which indicators do you monitor in youth treated with antipsychotic medication during a period lasting <u>longer than three months</u>?

Indicate in the table the frequency with which you commonly measure the indicators mentioned.
If you mark an indicator as "other," specify the frequency and the situations in which this occurs.

	Frequency					
Investigation	Never	< 1x per year	1x per year	2x per year	> 2x per year	Other, namely: ...
Laboratory indicators						
Lipid profile *Total cholesterol, HDL, LDL, TG*	○	○	○	○	○	○_____
Blood glucose *Glucose, HbA1c*	○	○	○	○	○	○_____
Prolactin	○	○	○	○	○	○_____
Antipsychotic blood level	○	○	○	○	○	○_____
Physical indicators						
Weight	○	○	○	○	○	○_____
Height	○	○	○	○	○	○_____
BMI	○	○	○	○	○	○_____
Fat mass / fat percentage	○	○	○	○	○	○_____
Waist and hip circumference	○	○	○	○	○	○_____
Heart rate	○	○	○	○	○	○_____
Blood pressure	○	○	○	○	○	○_____
QT interval / ECG	○	○	○	○	○	○_____
Other						
_____	○	○	○	○	○	○_____
_____	○	○	○	○	○	○_____

The next questions focus on monitoring in youth the laboratory and physical indicators mentioned in questions 1-3.

4. How many children and adolescents did you prescribe antipsychotic medication to during the past six months?

This includes all children with a first prescription or a repeat prescription.
Provide an estimate of the total number.

□ < 10
□ 10–20
□ > 20

5. Why do you start monitoring in youth treated (or start treatment) with antipsychotic medication?

Multiple answers possible.

□ Not applicable; I never monitor.
□ To choose the type of antipsychotic drug treatment.
□ To adjust the dose of antipsychotic drug treatment.
□ For early detection of changes in physical or laboratory indicators.
□ There are risk factors present before starting, like diabetes mellitus, a high BMI or familial hypercholesterolemia.
□ This is recommended by the guideline I follow.
□ Other, namely: .....

6. Why would you <u>not start monitoring</u> in youth treated (or start treatment) with antipsychotic medication?

Multiple answers possible.

- ☐ Not applicable; I always monitor.
- ☐ The child/adolescent does not wish to provide a blood sample (fear of needles).
- ☐ Monitoring is a burden for the child/adolescent.
- ☐ The parents/caretakers do not desire the child/adolescent to be monitored.
- ☐ Adherence to therapy might be lower when the child/adolescent or parents/caretakers are more aware of the possible adverse effects.
- ☐ Monitoring according to the guideline I follow is not necessary, in my opinion.
- ☐ Facilities to monitor are insufficiently available.
- ☐ Other, namely: .....

7. Why would you <u>stop monitoring</u> in youth treated with antipsychotic medication?

Multiple answers possible.

- ☐ The results of monitoring are in accordance with the reference values I utilize.
- ☐ The indicators monitored are stable.
- ☐ There are no symptoms of adverse effects.
- ☐ Treatment efficacy has been adjusted.
- ☐ The patient has become an adult (≥ 18 years old).
- ☐ The antipsychotic treatment has stopped.
- ☐ The child/adolescent does not wish to provide a blood sample anymore.
- ☐ Other, namely: .....

8. How is monitoring facilitated in your working environment?

Indicate in the table whether the facilitating factor is sufficiently or insufficiently available.

	Sufficient	Insufficient
Scale	○	○
Tape measure	○	○
Blood pressure monitor	○	○
Laboratory	○	○
Access to outcomes of laboratory indicators	○	○
Facilities to perform an ECG	○	○
Questionnaires regarding adverse effects	○	○
Ability to consult another specialist	○	○
Potential for referral if the child has a fear of needles	○	○
Other, namely:	○	○

9. Which percentage of youth to whom you prescribed antipsychotic medication in the last six months changed therapy because of the outcome of monitoring?

This includes all changes regarding therapy.
Provide an estimate of the percentage.

- ☐ This did not occur.
- ☐ < 25%
- ☐ 25–50%
- ☐ 50–75%
- ☐ > 75%

10. If the therapy changes because of the outcome of monitoring, what <u>type of change</u> is it?

Indicate the frequency of changes in the table.

	Frequency				
Change	Never	Rarely	Sometimes	Often	Always
Change in dosage	○	○	○	○	○
Switch between antipsychotics	○	○	○	○	○
Stop antipsychotic drug treatment (no switch)	○	○	○	○	○
Change in the remainder of pharmacotherapy	○	○	○	○	○
Referral to another specialist	○	○	○	○	○
Other advices, not medication *For example, diet or exercise*	○	○	○	○	○

11. Do you follow a guideline regarding monitoring for adverse effects of antipsychotics in youth?

□ No
□ Yes, namely:
  □ Accare guideline, monitoring for metabolic and endocrine adverse effects of antipsychotics (available at *Kenniscentrum Kinder- en Jeugdpsychiatrie*)
  □ National Institute for Health and Care Excellence (NICE) guidelines
  □ A local protocol, namely: .....
  □ Other, namely: .....

12. What could be improved regarding monitoring in youth treated with antipsychotics?

Background information

13. How many years have you been prescribing antipsychotic medication to youth?

☐ 0–1 year
☐ 2–5 years
☐ 6–10 years
☐ > 10 years

14. What is your specialty and in which type of heath care setting are you currently employed?

Specialty:

☐ Child and adolescent psychiatrist
☐ Child and adolescent psychiatrist in training
☐ Pediatrician
☐ Pediatrician in training
☐ General practitioner
☐ General practitioner in training
☐ Physician not in training to become a medical specialist
☐ Clinical nurse specialist
☐ Other, namely: .....

Health care setting:
Multiple answers possible.

☐ General hospital
☐ Private practice
☐ Mental health services, youth
☐ Mental health services, general
☐ Institution for patients with an intellectual disability
☐ Other, namely: .....

15. Additional remarks (optional)

Thank you for your cooperation!

Chapter 3.2

Monitoring of adverse drug reaction-related parameters in children and adolescents treated with antipsychotic drugs in psychiatric outpatient clinics

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ABSTRACT

Objectives

To assess the frequency of monitoring of adverse drug reaction (ADR) related parameters in children and adolescents treated with antipsychotic drugs in psychiatric outpatient clinics and the considerations when monitoring was not performed.

Methods

This retrospective follow-up study included 100 randomly selected outpatients aged ≤18 years who had a first prescription of an antipsychotic drug recorded in the electronic medical records of psychiatric outpatient clinics between 2014 and 2017. They were followed for up to 3 years. This study assessed the frequency of monitoring for physical parameters (weight, height, body mass index, waist circumference, pulse, blood pressure, and an electrocardiogram) and laboratory parameters (glucose, lipids, and prolactin) before the first prescription of an antipsychotic drug as well as during its use. Monitoring frequencies were stratified by the patient characteristics (sex, age, cardiovascular risk factors, and use of other psychotropic drugs), and by location of antipsychotic drug initiation (psychiatric outpatient clinic or elsewhere). Additionally, this study assessed the considerations mentioned in the medical records for not monitoring ADR-related parameters.

Results

Overall, physical parameters were monitored more frequently (weight: 85.9% during the first half-year) than laboratory parameters (glucose and cholesterol: both 23.5%). There were no significant differences in monitoring at least one physical as well as in monitoring at least one laboratory parameter during the baseline period and during the total follow-up of antipsychotic drug treatment between the patient characteristics. In total, 3% of the children and adolescents were never monitored for any physical parameter, and 54% were never monitored for any laboratory parameter. For a minority of the children (14.8%) who were never monitored for laboratory parameters, considerations were recorded in their medical records, including refusal by the child or parents and monitoring performed by the general practitioner or elsewhere.

Conclusion

Monitoring frequencies of ADR-related parameters in children and adolescents treated with antipsychotic drugs in psychiatric outpatient clinics varied and especially monitoring of laboratory parameters was infrequent. Considerations why monitoring was not performed were rarely recorded. The optimal method of monitoring and documentation thereof should become clear to optimize the benefit-risk balance of antipsychotic drug treatment for each child.

INTRODUCTION

Antipsychotic drugs are frequently prescribed to children and adolescents (hereafter referred to as *children*) to treat psychiatric disorders, including anxiety disorders, behavioral disorders, irritability associated with autism, tic disorders, and attention-deficit/hyperactivity disorder (ADHD).[1,2] Prescribing is commonly off-label because the evidence for efficacy of these drugs in this young and vulnerable population is scarce.[3,4] Furthermore, it is well-documented that antipsychotic drugs frequently cause bothersome and even severe adverse drug reactions (ADRs), including cardiometabolic, endocrine, and extrapyramidal adverse effects.[4,5] Examples of these adverse effects include weight gain, hypertension, gynecomastia, and parkinsonism.[4–6] These ADRs can differ in frequency and relative impact in children compared to adults.[7] Children seem to be more likely to experience somnolence during antipsychotic drug treatment than adults; moreover, the extent of weight gain was found to be greater in children.[8] Additionally, antipsychotic-induced hyperprolactinemia is more important in children because it may have an effect on pubertal development. ADRs can have both physical and emotional consequences and thereby negatively impact children's daily lives. Therefore next to monitoring efficacy, monitoring of ADRs is important to carefully evaluate and optimize the benefit-risk balance of antipsychotic drug treatment for each child.

The development of ADRs caused by antipsychotic drugs can be monitored through related parameters, including physical parameters (e.g., weight, height, body mass index (BMI), waist circumference, pulse, blood pressure, and heart examination) and laboratory parameters (e.g., glucose, lipids, and prolactin). Monitoring instructions of these parameters are available in clinical guidelines, and in regulatory drug product information such as the information leaflet.[9–12] Despite the existing guidelines and instructions, previous studies have shown a large variability in the monitoring frequencies of ADR-related parameters, and that the overall monitoring frequencies were suboptimal.[13–16] The majority of these studies used administrative databases from various settings, such as insurance companies or databases of general practitioners, but questionnaires about monitoring among prescribers have also been assessed.[14,16] In-depth assessments of the medical records of children treated with antipsychotic drugs is of added value in creating a complete overview of the total antipsychotic drug therapy of the individual child and what is actually monitored and recorded in daily clinical practice, including the considerations and choices made concerning (not) monitoring for ADR-related parameters.

The primary aim of this study was to assess the frequency of monitoring of ADR-related parameters in children treated with antipsychotic drugs in psychiatric outpatient clinics and the considerations when monitoring was not performed. The secondary aim was to compare differences in monitoring frequencies between sex,

age categories, children with and without cardiovascular risk factors, children who were and were not prescribed other psychotropic drugs, and children who started the antipsychotic drug treatment within the psychiatric outpatient clinics and those who started this therapy elsewhere.

METHODS

Setting, study population, and follow-up

This retrospective follow-up study included 100 randomly selected outpatients aged ≤18 years treated with an antipsychotic drug within Karakter, a large Dutch academic child and adolescent psychiatry organization that operates in 12 locations and offers clinical and outpatient therapy to children aged ≤18 years from across the Netherlands. Children are referred to this organization by, for example, general practitioners, for diagnosis and treatment of various psychiatric disorders, including autism spectrum disorder, ADHD, conduct disorders, depression, anxiety, compulsive disorders, eating disorders, and psychosis.

Patients were eligible for inclusion if they had a first prescription of an antipsychotic drug (ATC code N05A, excluding lithium [N05AN01]) within one of the psychiatric outpatient clinics of Karakter recorded in the electronic medical records between January 2014 and December 2017 and were prescribed an antipsychotic drug more than once. The date of this first prescription (index date) was defined as having no prescription of an antipsychotic drug recorded within the electronic medical records of these psychiatric (outpatient) clinics during the 6 months prior. Children could either have started the antipsychotic drug treatment within one of the psychiatric outpatient clinics of Karakter or elsewhere, for example in another psychiatric clinic. All included children were followed from the index date until the end of antipsychotic drug use recorded within the medical record, transfer out of practice, December 2018, or 3 years of follow-up, whichever came first. During follow-up, children could switch to another type of antipsychotic drug, and the period that a child was treated with an antipsychotic drug was considered to be continuous if the gap between the end date of one prescription and the start date of the next prescription was <3 months. The children included were never hospitalized within one of the psychiatric clinics of Karakter during follow-up.

Approval for this study was obtained from the organization's institutional review board (Karakter's committee for human research; reference number 148-18). A review by a medical ethics committee was not required because of the observational nature of the study with no involvement in the children's therapy or infringement of the psychological or physical integrity of the children. All data were recoded to secure privacy.

Data collection

The electronic medical records were stored within a clinical information system linked to an electronic drug prescription system, which were used by the healthcare professionals to access and update medical records. Within the clinical information system information regarding the child's psychiatric therapy could be consulted, including drug treatment, physical measurements, and the laboratory test results for blood glucose, lipids, and prolactin. The electronic drug prescription system also included information on the physical measurements weight, height, BMI, pulse, and blood pressure. Both systems were used to collect the data needed for this study.

Standard operational procedures (SOPs) and a checklist were used during data collection to ensure validity. Each SOP described the location of specific information in the electronic medical records, including patient characteristics, psychiatric and somatic diagnoses, diagnoses in family history, previous and current drug use, the (main) physician of the child, test requests, physical and laboratory test results, referrals, and the location of antipsychotic drug initiation. While collecting the data, patient numbers were recoded to ensure privacy.

Medical record review and data entry were conducted by two reviewers, and seven medical records were also reviewed by the first author to check for discrepancies. Discrepancies and ambiguities of all medical records were discussed and resolved by consensus with the first author as well as the additional co-authors.

Outcomes

Baseline information up to 31 days before the index date (start of antipsychotic drug) was collected, as well as data in 6-month timeframes (182 days) during follow-up. We assessed whether children were monitored for each ADR-related physical and laboratory parameter at least once during the baseline period, to assess if monitoring outcomes at the start of the antipsychotic drug treatment were known, and at least once during each fixed 6-month timeframe thereafter. When the follow-up time of antipsychotic drug use did not cover the complete final 6-month timeframe, this timeframe was excluded, and follow-up was censored at the end of the previous timeframe. The physical parameters included weight, height, BMI, waist circumference, pulse, blood pressure, and an electrocardiogram (ECG) and the laboratory parameters included glucose, cholesterol, low-density lipoproteins (LDL), high-density lipoproteins (HDL), triglycerides, and prolactin, based on the available clinical guidelines regarding monitoring.[9,10] A child was considered to be monitored in a certain timeframe in case the result of the monitoring parameter was recorded in the medical record of that child.

Determinants

Differences in monitoring frequencies of the ADR-related physical and laboratory parameters across the following patient characteristics were determined: 1) sex, 2) age categories (0-11 and 12-18 years old at the index date), 3) children with a cardiovascular risk factor at the index date and children without these risk factors, and 4) children who were prescribed other psychotropic drugs within the 6 months before, up to and including the index date, and children who were not prescribed other psychotropic drugs during this period. Additionally, differences in monitoring frequencies of the ADR-related physical and laboratory parameters were determined between children who started the antipsychotic drug treatment within the psychiatric outpatient clinics and those who started this therapy elsewhere. Cardiovascular risk factors were defined as having a recorded diagnosis of diabetes mellitus, hyperlipidemia, cardiovascular disorder, or overweight, hyperlipidemia according to the laboratory results or overweight according to the BMI measurement results. For the laboratory results, the reference values were included in the same document. The BMI measurement results were compared to the cutoff values described in a guideline for pediatricians.[17]

Considerations

Furthermore, this study assessed the considerations when monitoring of ADR-related physical and laboratory parameters was not performed during the antipsychotic drug treatment, which was defined as having no monitoring results included within the medical records.

Data analysis

Descriptive statistics were used to determine the percentage of children monitored for each physical and laboratory parameter at least once during the baseline period and every fixed 6-month timeframe thereafter. Additionally, the percentage of children was determined who had been monitored for at least one of the physical and at least one of the laboratory parameters during the baseline period and during the total follow-up period thereafter. Monitoring frequencies were stratified by sex, age categories, cardiovascular risk factors at baseline, use of other psychotropic drugs within the 6 months before, up to and including the index date, and location of initiation of the antipsychotic drug treatment. Relative risks (RRs) and 95% confidence intervals (95% CIs) were calculated when comparing strata. Statistical analyses were performed using SPSS Statistics version 25.

RESULTS

There were 1,877 outpatients who received a prescription of an antipsychotic drug within one of the psychiatric outpatient clinics between 2014 and 2017, who were prescribed an antipsychotic drug more than once, and who were never hospitalized within one of these psychiatric clinics during follow-up. One hundred children were randomly selected (Table 1), including only those who were ≤18 years of age at the index date and who did not have an antipsychotic drug prescription within these psychiatric (outpatient) clinics during the 6 months prior to the index date. The majority of the included children were male (79.0%), aged 6-11 years (52.0%), were prescribed risperidone at baseline (59.0%), had the initial antipsychotic drug prescription within one of the psychiatric outpatient clinics (85.0%), and were diagnosed with an autism spectrum disorder (80.0%).

Table 1. Characteristics of the study population (n = 100)

Characteristic	n	(%)
Sex		
Females	21	(21.0)
Males	79	(79.0)
Age at index date (years)		
0-5	9	(9.0)
6-11	52	(52.0)
12-18	39	(39.0)
Year of index date		
2014	27	(27.0)
2015	29	(29.0)
2016	24	(24.0)
2017	20	(20.0)
Total duration of follow-up (years) [$]		
< 0.5	15	(15.0)
0.5-1.0	19	(19.0)
1.0-1.5	19	(19.0)
1.5-2.0	11	(11.0)
2.0-2.5	7	(7.0)
2.5-3.0	9	(9.0)
3.0	20	(20.0)

Table 1. continued

Characteristic	n	(%)
Antipsychotic drug prescribed (at index date)		
Risperidone	59	(59.0)
Aripiprazole	22	(22.0)
Pipamperone	10	(10.0)
Olanzapine	4	(4.0)
Quetiapine	4	(4.0)
Haloperidol	1	(1.0)
Initial antipsychotic drug prescription		
Within the psychiatric clinic	85	(85.0)
Elsewhere	15	(15.0)
Psychiatric disorders (ever before index date) *		
Autism spectrum disorder	80	(80.0)
Attention-deficit / hyperactivity disorder	47	(47.0)
Intellectual disability	17	(17.0)
Anxiety disorder (incl. OCD, PTSD, phobia)	16	(16.0)
Mood disorder	11	(11.0)
Tic disorder	11	(11.0)
Behavioral disorder	9	(9.0)
Eating disorder	4	(4.0)
Sleeping disorder	4	(4.0)
Other	23	(23.0)
> 1 psychiatric disorder (included above)	76	(76.0)
Somatic disorders / problems (ever before index date) *		
Genetic / congenital / metabolic	15	(15.0)
Allergies / asthma / eczema	11	(11.0)
Overweight / obesity	11	(11.0)
Gastrointestinal / incontinence	7	(7.0)
Epileptic disorder	5	(5.0)
Urinary	5	(5.0)
Fetal alcohol syndrome / neonatal abstinence syndrome	4	(4.0)
Underweight	3	(3.0)
Hyperlipidemia	2	(2.0)
Cardiovascular	1	(1.0)
Other	9	(9.0)

Table 1. continued

Characteristic	n	(%)
Psychotropic drug use (6 months before index date) *		
Stimulants and atomoxetine	33	(33.0)
Hypnotics / sedatives	26	(26.0)
Antidepressants	6	(6.0)
Other (clonidine and lithium)	7	(7.0)
Somatic drug use (6 months before index date) *		
Antihistamines	7	(7.0)
Oral inhalers and montelukast	6	(6.0)
Antiepileptic drugs	3	(3.0)
Other	21	(21.0)

Index date: first prescription of an antipsychotic drug recorded in the electronic medical records of the psychiatric outpatient clinic.
$ Total duration of follow-up (years): mean 1.6, median 1.4.
* Recorded in the electronic medical records of the psychiatric clinic, up to and including the index date; several children and adolescents were diagnosed with more than one disorder and used more than one drug.
OCD, obsessive-convulsive disorder; PTSD, post-traumatic stress disorder.

Monitoring of physical and laboratory parameters

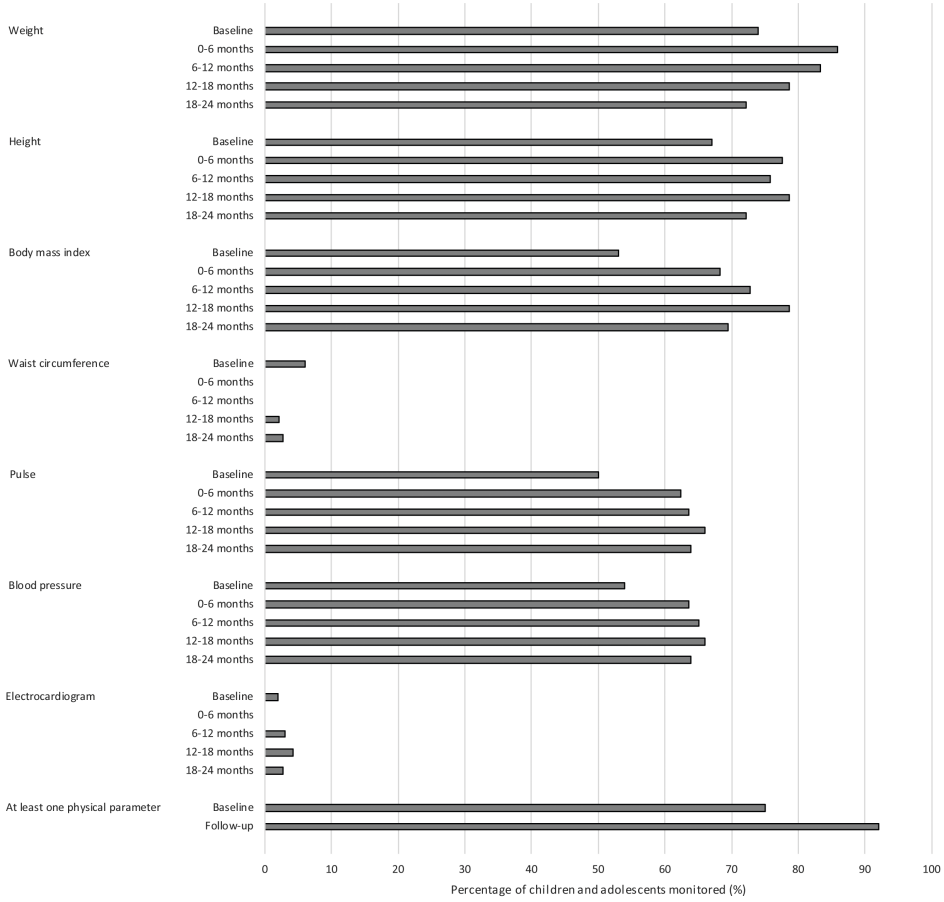
Overall, physical parameters were monitored more frequently than laboratory parameters (Figures 1A,B). The physical parameter weight was monitored most frequently in children during the baseline period (74.0%) compared to the other physical and laboratory parameters. After 6 months, 85 children were still treated with an antipsychotic drug, and the physical parameters monitored most frequently in these children during this first half-year of antipsychotic drug treatment were weight (n = 73; 85.9%) and height (n = 66; 77.6%), and the laboratory parameters monitored most frequently were glucose and cholesterol (both n = 20; 23.5%). None of the children were monitored for waist circumference or ECG during the first half-year of treatment.

In total, 75.0% of the children were monitored at least once for one of the physical parameters during the baseline period and 92.0% during the total follow-up of antipsychotic drug treatment thereafter (Figure 1A). Additionally, 11.0% of the children were monitored at least once for one of the laboratory parameters during the baseline period and 40.0% during the total follow-up of antipsychotic drug treatment thereafter (Figure 1B). Of those children who were not monitored during the baseline period for any physical parameter (n = 25), three (12.0%) were monitored for at least one physical parameter within the first week of antipsychotic drug treatment. Of those children who were not monitored during the baseline

period for any laboratory parameter (n = 89), nine (10.1%) were monitored for at least one laboratory parameter within the first week of antipsychotic drug treatment.

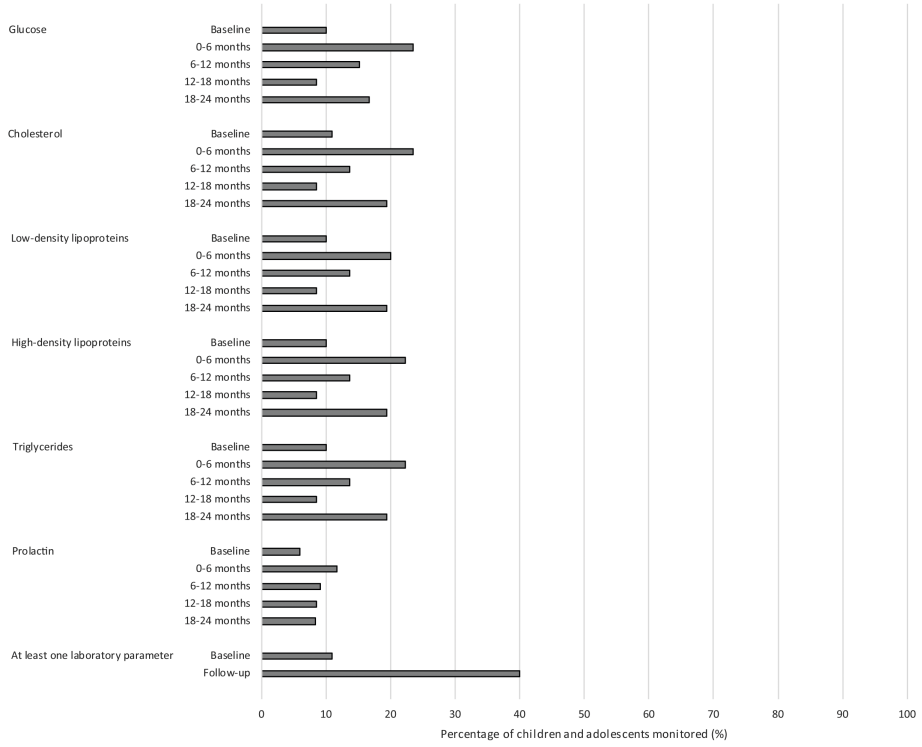
Figure 1. Monitoring of adverse drug reaction-related parameters in children and adolescents treated with antipsychotic drugs in psychiatric outpatient clinics.

A. Monitoring of physical parameters



Total number of children and adolescents: baseline period n = 100; 0-6 months n = 85; 6-12 months n = 66; 12-18 months n = 47; 18-24 months n = 36.

B. Monitoring of laboratory parameters



Total number of children and adolescents: baseline period n = 100; 0-6 months n = 85; 6-12 months n = 66; 12-18 months n = 47; 18-24 months n = 36.

Determinants

There were no significant differences in monitoring of at least one physical parameter as well as in monitoring of at least one laboratory parameter during the baseline period and during the antipsychotic drug treatment thereafter between the patient characteristics, including sex, age categories, cardiovascular risk factors at the start of antipsychotic drug treatment, and use of other psychotropic drugs within the 6 months before the start of antipsychotic drug treatment (Table 2). There were also no significant differences between children who started the antipsychotic drug treatment within the psychiatric outpatient clinics and those who started this therapy elsewhere.

Table 2. Monitoring of adverse drug reaction-related parameters in children and adolescents treated with antipsychotic drugs in psychiatric outpatient clinics: stratified by sex, age, cardiovascular risk factors, use of other psychotropic drugs, and location of antipsychotic drug initiation.

		Physical parameters				Laboratory parameters			
		Baseline		Follow-up		Baseline		Follow-up	
	n	%	RR [95% CI]	%	RR [95% CI]	%	RR [95% CI]	%	RR [95% CI]
Sex									
Female	21	66.7	1 (ref)	85.7	1 (ref)	9.5	1 (ref)	23.8	1 (ref)
Male	79	77.2	1.2 [0.8-1.6]	93.7	1.1 [0.9-1.3]	11.4	1.2 [0.3-5.1]	44.3	1.9 [0.8-4.2]
Age									
0-11 years old	61	77.0	1 (ref)	96.7	1 (ref)	16.4	1 (ref)	34.4	1 (ref)
12-18 years old	39	71.8	0.9 [0.7-1.2]	84.6	0.9 [0.8-1.0]	2.6	0.2 [0.0-1.2]	48.7	1.4 [0.9-2.3]
Cardiovascular risk factor [#]									
No	86	74.4	1 (ref)	91.9	1 (ref)	10.5	1 (ref)	40.7	1 (ref)
Yes	14	78.6	1.1 [0.8-1.4]	92.9	1.0 [0.9-1.2]	14.3	1.4 [0.3-5.7]	35.7	0.9 [0.4-1.9]
Other psychotropic drugs [$]									
No	48	72.9	1 (ref)	91.7	1 (ref)	14.6	1 (ref)	41.7	1 (ref)
Yes	52	76.9	1.1 [0.8-1.3]	92.3	1.0 [0.9-1.1]	7.7	0.5 [0.2-1.7]	38.5	0.9 [0.6-1.5]

Table 2. Continued

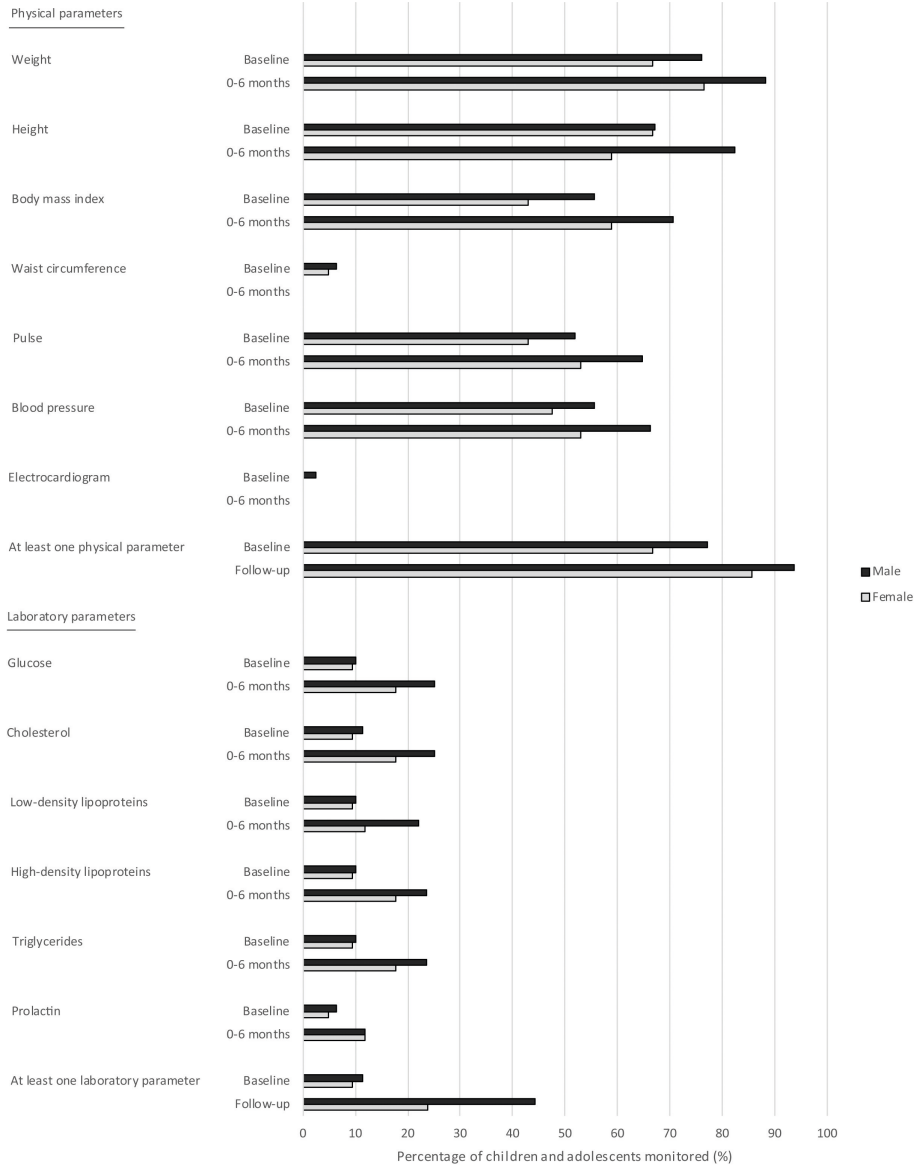
		Physical parameters				Laboratory parameters			
		Baseline		Follow-up		Baseline		Follow-up	
	n	%	RR [95% CI]	%	RR [95% CI]	%	RR [95% CI]	%	RR [95% CI]
Initiation at the psychiatric clinic									
No	15	60.0	1 (ref)	86.7	1 (ref)	6.7	1 (ref)	33.3	1 (ref)
Yes	85	77.6	1.3 [0.8-2.0]	92.9	1.1 [0.9-1.3]	11.8	1.8 [0.2-12.8]	41.2	1.2 [0.6-2.6]

Children and adolescents who were monitored for at least one physical and for at least one laboratory parameter during the baseline period and during the total follow-up of antipsychotic drug treatment thereafter.
Baseline period: a maximum of 1 month before the first prescription of an antipsychotic drug in the psychiatric outpatient clinic, up to and including the date of this first prescription.
cardiovascular risk factors at baseline: diagnosis for overweight or overweight according to the body mass index measurements (n = 11), diagnosis for hyperlipidemia or hyperlipidemia according to the laboratory results (n = 2), diagnosis for a cardiovascular disorder (n = 1), diagnosis for diabetes mellitus (n = 0).
$ Use of other psychotropic drugs within the 6 months before the first prescription of an antipsychotic drug within the psychiatric outpatient clinic, up to and including the date of the first prescription.
n, number of children and adolescents; RR [95%CI], relative risk [95% confidence interval].

Assessing each physical and laboratory parameter separately, there were only few significant differences found regarding the monitoring frequency during the baseline period and during the first 6 months of antipsychotic drug treatment within one of the psychiatric outpatient clinics. There were no significant differences in monitoring between males and females (Figure 2A), but there were significant differences between the two age categories, as the physical parameters height and blood pressure were monitored relatively less frequently in children aged 12-18 years than in children aged 0-11 years (RR [95% CI]: 0.7 [0.6-1.0] and 0.7 [0.4-1.0], respectively) during the first 6 months of antipsychotic drug treatment (Figure 2B). Overall, children who were treated with other psychotropic drugs within the 6 months before the start of the antipsychotic drug treatment were monitored relatively more frequently during the baseline period and during the first 6 months thereafter for the majority of physical parameters compared to children not treated with other psychotropic drugs, but the only significant difference was found in monitoring for pulse during the baseline period (RR [95% CI]: 1.6 [1.1-2.5]). There were also no significant differences in monitoring the physical as well as the laboratory parameters when assessing only the psychotropic drugs prescribed within one of the psychiatric outpatient clinics and not elsewhere, for example by the general practitioner. Most parameters were monitored relatively more frequently when the antipsychotic drug treatment started within one of the psychiatric outpatient clinics included compared to elsewhere during the baseline period and during the first 6 months of antipsychotic drug treatment. Nevertheless, the only significant differences were monitoring for weight and waist circumference, as weight was monitored relatively more often in children who started the antipsychotic drug treatment within one of the psychiatric outpatient clinics compared to elsewhere (RR [95% CI]: 1.5 [1.0-2.3]) during the first 6 months of antipsychotic drug treatment within one of the psychiatric outpatient clinics, and waist circumference was monitored relatively less often in children who started the antipsychotic drug treatment within one of the psychiatric outpatient clinics compared to elsewhere (RR [95% CI]: 0.2 [0.0-0.8]) during the baseline period.

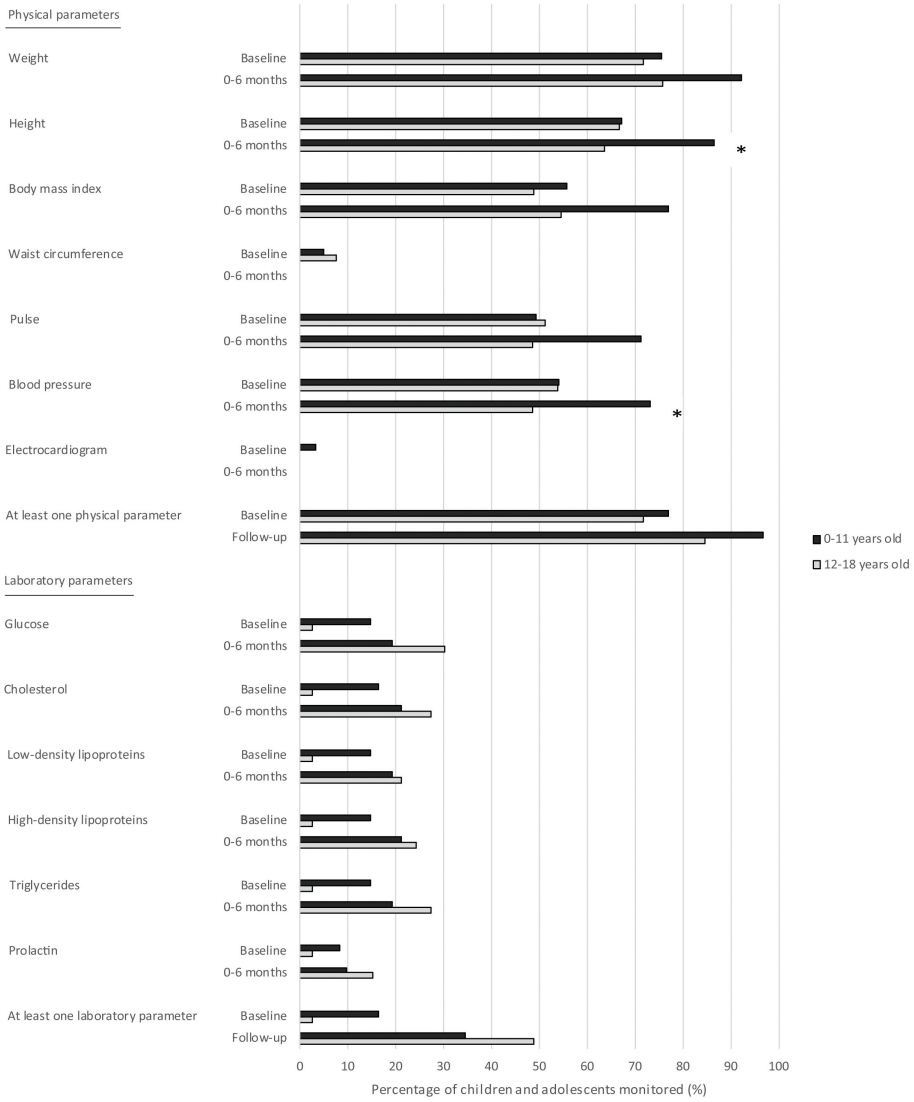
Figure 2. Monitoring of adverse drug reaction-related parameters in children and adolescents treated with antipsychotic drugs in psychiatric outpatient clinics: stratified by sex and age.

A. Stratification by sex



Total number of children and adolescents: Male: baseline period n = 79; 0-6 months n = 68; Female: baseline period n = 21; 0-6 months n = 17.

B. Stratification by age



Total number of children and adolescents: 0-11 years old: baseline period n = 61; 0-6 months n = 52; 12-18 years old: baseline period n = 39; 0-6 months n = 33.
Baseline period: a maximum of one month before the first prescription of an antipsychotic drug in the psychiatric outpatient clinic, up to and including the date of this first prescription.
***** Significant difference; $p < 0.05$.

Considerations

Of all included children, three were never monitored for any physical parameter during the baseline period or during the follow-up of antipsychotic drug treatment thereafter, and 54 were never monitored for any laboratory parameter. Regarding the three children who were never monitored for physical parameters, considerations why monitoring was not performed were not mentioned in their medical records. For eight of the 54 children (14.8%) who were never monitored for laboratory parameters, considerations for this lack of monitoring results were recorded in their medical records. The considerations or reasons included refusal by the child (e.g., fear of needles; n = 4) or parents (n = 1) and monitoring performed by the general practitioner or elsewhere (n = 4), but these results were not recorded in the medical records of the psychiatric outpatient clinic.

In the medical records of children who were monitored at least once for physical parameters during the baseline period or during the follow-up of antipsychotic drug treatment (n = 97), refusal by the child was mentioned in two medical records (2.1%). It was mentioned within several medical records that monitoring of physical parameters was also performed by the parents (n = 12; 12.4%), general practitioner (n = 10; 10.3%), or pediatrician (n = 2; 2.1%), though it was not clear if these monitoring results were always recorded in the medical records of the psychiatric outpatient clinics. In the medical records of children who were monitored at least once for laboratory parameters during the baseline period or during follow-up (n = 46), considerations or reasons for a delay in monitoring or a lack of results included also refusal by the child (n = 5; 10.9%), delay caused by the parents (n = 2; 4.3%), monitoring of glucose by the parents (n = 1; 2.2%), or monitoring performed elsewhere (n = 5; 10.9%), but the results were not recorded in the medical records of the psychiatric outpatient clinic.

DISCUSSION

Although most physical parameters were monitored more frequently than laboratory parameters in children treated with antipsychotic drugs in psychiatric outpatient clinics, the monitoring frequencies for the majority of the parameters were low. There were no significant differences in monitoring of ADR-related parameters between sex and between children with and without cardiovascular risk factors at the start of the antipsychotic drug treatment, and only a few between age categories (height and blood pressure), children who did or did not use other psychotropic drugs within the 6 months before the start of the antipsychotic drug treatment (pulse), and between the initiation of the antipsychotic drug treatment at the psychiatric outpatient clinics or elsewhere (weight and waist circumference). The considerations when there were no monitoring results included in the medical

records were only occasionally reported, as, for example, this was only mentioned for 14.8% of the children who were never monitored for laboratory parameters. Considerations mentioned included refusal by the child or parents and monitoring performed by the general practitioner or elsewhere.

Although previous studies have shown differences in monitoring frequencies in children treated with antipsychotic drugs, it is clear that the monitoring frequencies were suboptimal.[13,15,16,18] Overall, it has been shown that the physical parameter weight was monitored more frequently in children treated with antipsychotic drugs compared to the laboratory parameters glucose and lipids, and waist circumference was monitored much less, which is in line with the results of this current study.[14,15,19]

Some differences in monitoring frequencies across sex and age categories were indicated in this study. Although this current study showed no significant differences between sex, it seemed that boys were monitored relatively more frequently than girls. This study demonstrated significant differences between age categories (0-11 and 12-18 years) in monitoring for the physical parameters height and blood pressure, but there were no significant differences in monitoring for laboratory parameters. However, higher monitoring frequencies of laboratory parameters in older children were demonstrated in previous studies.[20,21] This result could also have been expected in the current study, as these differences in monitoring frequencies of laboratory parameters could be due to the fear of needles, which is generally more common in younger children.[22]

Especially the monitoring frequencies of the laboratory parameters were low. Monitoring instructions of parameters are available in clinical guidelines, but these guidelines differ in which parameters they recommend to monitor and the frequency of monitoring.[9–11,23] Although there is no national clinical guideline in the Netherlands for monitoring of ADR-related parameters in children treated with antipsychotic drugs, the guideline of Accare, a large academic mental health organization for child and adolescent psychiatry in the northern part of the Nederlands, is widely used by other Dutch healthcare professionals and is published on the national website for child and adolescent psychiatry (https://www.kenniscentrum-kjp.nl/).[9] Strict use of this guideline varies among prescribers, also within Karakter. The low monitoring frequencies of the laboratory parameters could be due to the recommendation of this guideline to monitor the parameters glucose and lipids only at baseline and every 6 months thereafter when there are risk factors present. One of these risk factors is overweight. However, no significant differences were shown by this study between children with and without cardiovascular risk factors, including overweight. Overweight was the most reported cardiovascular risk factor within this study. The risk factors hyperlipidemia and diagnosis for a cardiovascular disorder were only reported in few medical records, and diabetes mellitus in none. This could

be because these disorders are rare in children, or this information was not well-reported in the medical records and therefore missing.

Previous studies have shown suboptimal monitoring frequencies in children treated with antipsychotic drugs and low compliance to monitoring guidelines.[15,20,24] Improvement in monitoring practices is needed, which is seen not only in children treated with antipsychotic drugs, but also the monitoring frequencies for adults treated in psychiatric outpatient clinics have been shown to be suboptimal according to the guidelines.[25] Additionally, low monitoring frequencies are not only related to antipsychotic drug use, as low monitoring frequencies and poor adherence to clinical guidelines have also been demonstrated concerning other psychotropic drugs, including lithium, as well as somatic drugs.[26–28]

As this study showed only minor differences in monitoring frequencies between patient characteristics, including sex, age categories, and children with and without risk factors present, and suboptimal monitoring frequencies were also shown by other studies including adults and other types of drugs, the reasons for suboptimal monitoring might be with the healthcare professionals (or the system) or children and caregivers themselves. Suboptimal monitoring by the healthcare professionals could be caused by the lack of a clear national clinical guideline, insufficient collaboration with other healthcare professionals, low confidence about monitoring, a lack of a reminder system or insufficient access to the equipment needed, for example a blood pressure machine.[29] Despite the lack of a national guideline, the majority of the prescribers of antipsychotic drugs to children are aware that they should monitor for ADRs.[14] However, when collaborating with other health care professionals, it is not always clear who is responsible to monitor for ADRs.[29–31] As shown in this current study, children could also be monitored by the general practitioner or pediatrician, though it was not always clear which exact parameters were monitored elsewhere and if the results were recorded in the medical records of the psychiatric outpatient clinics, since the electronic systems were not linked. A gap between monitoring for ADRs and the rest of the antipsychotic drug treatment is concerning, as it could lead to poor monitoring, undetected abnormalities in ADR-related physical and laboratory parameters, and insufficient follow-up of the antipsychotic drug treatment. An electronic system for medical records could enhance the monitoring practices by more easily sharing monitoring results and defining whose responsibility it is to monitor the children.[29] Electronic medical records do also facilitate as they improve the quality of outpatient clinic notes, including information about ADRs and follow-up information.[32] However, documentation quality varies between healthcare professionals and type of care measure in regard to medication, drug allergies, and compliance with guidelines, as also seen in this current study.[33] Electronic systems should be equipped to suit the needs of healthcare professionals in the evaluation and monitoring of ADRs in children treated with antipsychotic drugs.[34] For example,

this electronic system should also include a reminder system, not only to remind the healthcare professional that monitoring should be performed, but also to assess the parameters outcomes, for example laboratory parameters, on a later moment in time. Furthermore, the children and the caregivers play an important and active role in optimizing monitoring practices. Barriers related to the children or caregivers are refusal by the child, for example because of a fear of needles, as also shown in this study, or the caregivers who resist or simply forget to obtain the laboratory tests.[35] Clear instructions and information tailored to the patient would improve monitoring practices.[36] Additionally, it is important that the healthcare professional is aware of the barriers present and can anticipate the specific situation.

A strength of this study was that by reviewing the electronic medical records, a complete overview was gained of the total antipsychotic drug therapy of the individual child in the psychiatric outpatient clinics. Medical records review and data entry were conducted by only two reviewers, who used SOPs and the checklist to gather the information needed, which ensured that they gathered information consistently and no important files in the medical records were missed. However, this study also has some limitations. This study included a relatively small number of children in one mental healthcare institution in the Netherlands, although there were multiple locations involved. Especially the numbers when separating in different patient characteristics and the location of initiation of the antipsychotic drug treatment were small. To compare these groups was the secondary aim of the study. More research is needed to detect differences between those groups. The diagnoses (Table 1) were those reported in the medical records and we did not validate these diagnoses. However, this does not influence the results of this study as a child treated with an antipsychotic drug should be monitored regardless of the diagnosis. Fifteen children were prescribed an antipsychotic drug elsewhere before they were transferred to one of the psychiatric outpatient clinics, which could lead to a difference in documentation history compared to the children who started the antipsychotic drug treatment within the psychiatric outpatient clinics. Some children did not have 1 month of valid data available before the index date. Data collected depended on what was reported within the records, and notes could be missing, unclear, or incomplete. However, for this study also the free texts within a medical record were taken into account. Even if missing or unclear data has led to an underestimation of the monitoring frequencies, this would also deteriorate the quality and completeness of the medical records in the psychiatric outpatient clinics in daily clinical practice, and could lead to an incomplete transfer of information to other internal and external healthcare professionals.

Clinical implications

By monitoring children treated with antipsychotic drugs, abnormalities in ADR-related physical and laboratory parameters can come to light, and interventions can be performed to optimize the benefit-risk balance of the antipsychotic drug treatment for each child, including lowering the dosage, switching to another drug, a referral to a dietitian or consulting a pediatrician. When monitoring is suboptimal, this could cause severe risks, as abnormalities in blood glucose and a high body weight could result in the development of diabetes mellitus, and abnormalities in blood prolactin levels could lead to gynecomastia and galactorrhea.[37,38] On the other hand, when the monitoring frequency is excessive, this not only increases the healthcare costs, causes unneeded time investments and an administrative burden for the healthcare professionals, this can also impact the child's quality of life, considering the fear of needles and the constant reminder of the psychiatric disorder with which the child has been diagnosed. Further research is needed to gain knowledge about the optimal method of monitoring for ADR-related parameters in children, which should be captured in a clear national clinical guideline to prevent children from developing severe ADRs and to optimize the benefit-risk balance in the individual child.

CONCLUSION

Overall, monitoring frequencies of ADR-related parameters in children treated with antipsychotic drugs in psychiatric outpatient clinics varied and especially monitoring of the laboratory parameters was low. There were no prominent differences in monitoring between patient characteristics, for example across sex and age categories. Considerations why monitoring was not performed were rarely recorded within the medical records. By gaining more knowledge concerning the optimal frequency of monitoring and the facilitators and barriers for monitoring in psychiatric outpatient clinics as well as for each child, monitoring practices could be improved. Monitoring leads to knowledge about the effects of the antipsychotic drug treatment in the individual child, which is essential to evaluate and improve the benefit-risk balance of the therapy.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Chapter 3.3

Monitoring of adverse drug reaction-related parameters in children, youth, and young adults prescribed antipsychotic drugs by general practitioners

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ABSTRACT

Objective

The aim of the study was to assess monitoring of adverse drug reaction (ADR)-related parameters in children, youth, and young adults treated with second-generation antipsychotic drugs (SGAs) prescribed by general practitioners (GPs).

Methods

This retrospective follow-up study included children, youth, and young adults aged 0 - 24 years, who had an initial prescription of an SGA recorded in the Clinical Practice Research Datalink between 2000 and 2017, and who were prescribed an SGA more than once for a duration of at least 6 months. It included an assessment of which ADR-related physical parameters (weight, height, body-mass index, waist circumference, pulse, blood pressure, and heart examination) and laboratory parameters (glucose, HbA1c, lipids, and prolactin) were monitored in children, youth, and young adults at least once every 6-month period, stratified by sex, age categories, and calendar years.

Results

In total, 7,006 patients were included and the mean duration of follow-up was 1.6 years. Monitoring frequencies of all parameters were below 25%. Blood pressure and weight were monitored in 23.6% and 23.4%, respectively, of all children, youth, and young adults during the first half year; waist circumference was monitored in 0.2%. Females were monitored more often than males, some differences between age categories were observed, and monitoring frequencies increased after 2000, but did not exceed 35% in any year.

Conclusion

Monitoring frequencies of ADR-related parameters in children, youth, and young adults treated with SGAs prescribed by a GP were low. Monitoring in primary care should be improved to enable a better evaluation of the benefit-risk balance during antipsychotic drug therapy.

INTRODUCTION

Antipsychotic drugs are frequently prescribed to children, youth, and young adults (hereafter referred to as youth) to treat psychiatric disorders, including psychotic symptoms, conduct disorders, irritability associated with autism, and attention-deficit/hyperactivity disorder.[1,2] Although most often prescribed by psychiatrists, other physicians also have a prominent role in treating youth with antipsychotic drugs.[2–5] General practitioners (GPs) can initiate antipsychotic drug therapy in youth, but prescribing antipsychotics by GPs most often concerns continuation of therapy started by specialists.

Regardless of the specialty of the prescriber, careful evaluation and monitoring of benefits and risks of antipsychotic drugs are especially important in youth since off-label prescribing is common, and this young population is vulnerable.[6] Monitoring risks of antipsychotic drugs in the individual youth is important because these drugs can frequently cause severe adverse drug reactions (ADRs), including extrapyramidal, cardiometabolic, and endocrine adverse effects.[7–11] Examples of these adverse effects are parkinsonism, weight gain, hypertension, tachycardia, development of diabetes mellitus, and gynecomastia. The safety risks in youth are not the same as in adults.[12] For example, the extent of weight gain induced by antipsychotic drugs was found to be even greater in youth than in adults.[13,14] Additionally, gynecomastia can also have a high emotional impact on boys during puberty.

No antipsychotic drug is free of ADRs, and second-generation antipsychotics (SGAs) can cause different ADRs than first-generation antipsychotics. Generally, SGAs have a lower risk of extrapyramidal adverse effects than first-generation antipsychotics, but can cause more metabolic adverse effects.[15] In particular, prescribing SGAs in youth requires regular monitoring to detect cardiometabolic adverse effects and prevent harm. Monitoring frequencies in youth treated with antipsychotic drugs have been studied in clinical practice and have appeared to be suboptimal, but the degree to which GPs monitor youth treated with antipsychotic drugs is unclear.[16–20]

Clinical guidelines are available to provide information regarding monitoring and evaluation of ADRs of SGAs. These ADRs can be monitored through related parameters, including physical – weight, height, body-mass index (BMI), waist circumference, pulse, blood pressure, and heart examination – and laboratory – glucose, HbA1c, lipids, and prolactin – parameters. There are differences between guidelines on which parameters they advise to monitor and the frequency of monitoring.[21,22] In the United Kingdom, the National Institute for Health and Care Excellence (NICE) guideline provides guidance and advice on how to monitor ADR-related parameters in children and young people treated with antipsychotic drugs.[23]

The NICE guideline is available to all health care providers and advises, for example, monitoring weight at baseline, weekly for the first 6 weeks, at 12 weeks, and every 6 months thereafter. Although most prescribers of antipsychotic drugs to youth are aware of the existence of monitoring guidelines,[24] previous studies have illustrated that in daily practice not all youth were monitored,[16–20] and practices varied regarding which parameters require monitoring and how frequently it was done.[25]

The aim of this study was to assess monitoring of ADR-related parameters in youth treated with SGAs prescribed by GPs. Additionally, differences in monitoring across sex, age categories, and calendar years were determined.

METHODS

Setting

Data for this study were obtained from the Clinical Practice Research Datalink (CPRD), which holds electronic medical records from 674 general practices in the United Kingdom.[26] Although not all practices in the United Kingdom participate, the data are representative for the whole population in terms of sex, age, and ethnicity.[26] The database provides detailed information on demographics, clinical events, drug prescriptions, referrals, hospital admissions, and tests. Data collection began in January 1987, and over 11 million persons are currently included.[26] Approval for this study was obtained from the CPRD Independent Scientific Advisory Committee, reference number: 17_052R2A.

Study population and design

Youth aged 0 - 24 years, who had an initial prescription of an SGA (BNF code 04020102; Supplementary Table S1) recorded in the CPRD database between January 2000 and December 2017, and who were prescribed an SGA more than once for a duration of at least 6 months were included. This initial prescription by the GP could be the start of the antipsychotic drug therapy as well as continuation of the treatment started by specialists. Youth were followed from the date of their first prescription of an SGA (index date) until the end of SGA prescriptions, age >24 years, transfer out of the practice, last data collection for the practice, or date of death, whichever came first. Youth needed to have at least 6 months of valid data available before the index date to be included in this study. If they were again prescribed an SGA after the end of follow-up, this second episode was not included.

This was a retrospective follow-up study, and the individual follow-up time for all youth was divided into fixed time frames of 6 months (182 days). The theoretical duration of antipsychotic drug usage was calculated by dividing the amount prescribed by the dosage regimen for each prescription. When the theoretical

duration of antipsychotic drug usage was unknown, <1 day or >365 days, the overall median duration of a prescription was utilized, which was 28 days for oral medication and 14 days for intramuscular medication. Youth could switch to another type of SGA during follow-up, and the period that youth were treated with SGAs was considered to be continuous if the gap between the theoretical end date of one prescription and the start date of the next prescription was less than 90 days. When the follow-up time of antipsychotic drug usage did not cover the complete final 6-month time frame, this time frame was excluded, and follow-up was censored at the end of the previous time frame.

Outcome and determinants

It was assessed whether youth were monitored for ADR-related parameters at least once during each fixed 6-month time frame based on the NICE guideline, including monitoring of children and young people treated with antipsychotic drugs (CG155).[23] These parameters included both physical – weight, height, BMI, waist circumference, pulse, blood pressure, and heart examination – and laboratory – glucose, HbA1c, lipids, and prolactin – parameters. Monitoring of BMI was included when reported as such in the database and was not included when height and weight were both measured, but BMI was lacking. Code lists of physical and laboratory parameters were composed (Supplementary Table S2) and checked by a second author (E.R.H.).

Differences in monitoring frequencies of ADR-related physical and laboratory parameters were determined across sex, age categories (0-11, 12-18, and 19-24 years old), and calendar years.

Data analyses

Descriptive statistics were used to determine the percentage of youth who had been monitored for physical and laboratory parameters at least once every 6 months when prescribed an SGA. Data were stratified by sex, age categories, and calendar years. Relative risks (RRs) and 95% confidence intervals (95% CIs) were calculated when comparing strata. Statistical analyses were performed with SAS 9.4.

RESULTS

There were 15,342 youths aged 0 - 24 years who received an initial prescription of an SGA between 2000 and 2017 and were prescribed an SGA more than once. After excluding youth with less than 6 months of valid data before the index date and a follow-up time of less than 6 months, 7,006 youths were included in this study (Table 1). Most were male (n = 4,330; 61.8%), aged 19 - 24 years (n = 3,781; 54.0%), and were prescribed risperidone at baseline (n = 2,932; 41.8%).

Table 1. Characteristics of the study population (n = 7,006)

Characteristic	n	(%)
Sex		
Females	2,676	(38.2)
Males	4,330	(61.8)
Age (at index date; years)		
0-5	29	(0.4)
6-11	657	(9.4)
12-18	2,539	(36.2)
19-24	3,781	(54.0)
Year of index date		
2000-2005	1,618	(23.1)
2006-2011	2,706	(38.6)
2012-2017	2,682	(38.3)
Duration of second-generation antipsychotic drug use [a]		
< 12 months	2,828	(40.4)
12-24 months	2,199	(31.4)
≥ 24 months	1,979	(28.2)
Second-generation antipsychotic drug (at index date) [b]		
Risperidone	2,932	(41.8)
Quetiapine	1,742	(24.9)
Olanzapine	1,707	(24.4)
Aripiprazole	528	(7.5)
Other	115	(1.6)
Disorders (ever before index date) [c]		
Psychiatric disorders		
Depression	2,649	(37.8)
Anxiety disorder	1,927	(27.5)
Psychotic disorder	1,282	(18.3)
Sleep disorder	1,199	(17.1)
Attention-deficit/hyperactivity disorder	968	(13.8)
Autism spectrum disorder	920	(13.1)
Eating disorder	396	(5.7)
Bipolar disorder	239	(3.4)
Somatic disorders		
Overweight	204	(2.9)
Diabetes mellitus	45	(0.6)
Dyslipidaemia	4	(0.1)

Table 1. Continued

Characteristic	n	(%)
Drug use (half year before index date)[c]		
Cardiovascular		
Antidiabetics (not insulin)	22	(0.3)
Antilipemics	7	(0.1)
Insulins	30	(0.4)
Central nervous system		
Antidepressants	2,801	(40.0)
Antipsychotics (excl. second-generation antipsychotics)	416	(5.9)
Anxiolytics /hypnotics /benzodiazepines	1,763	(25.2)
Mood stabilizers	382	(5.5)
Stimulants	592	(8.4)

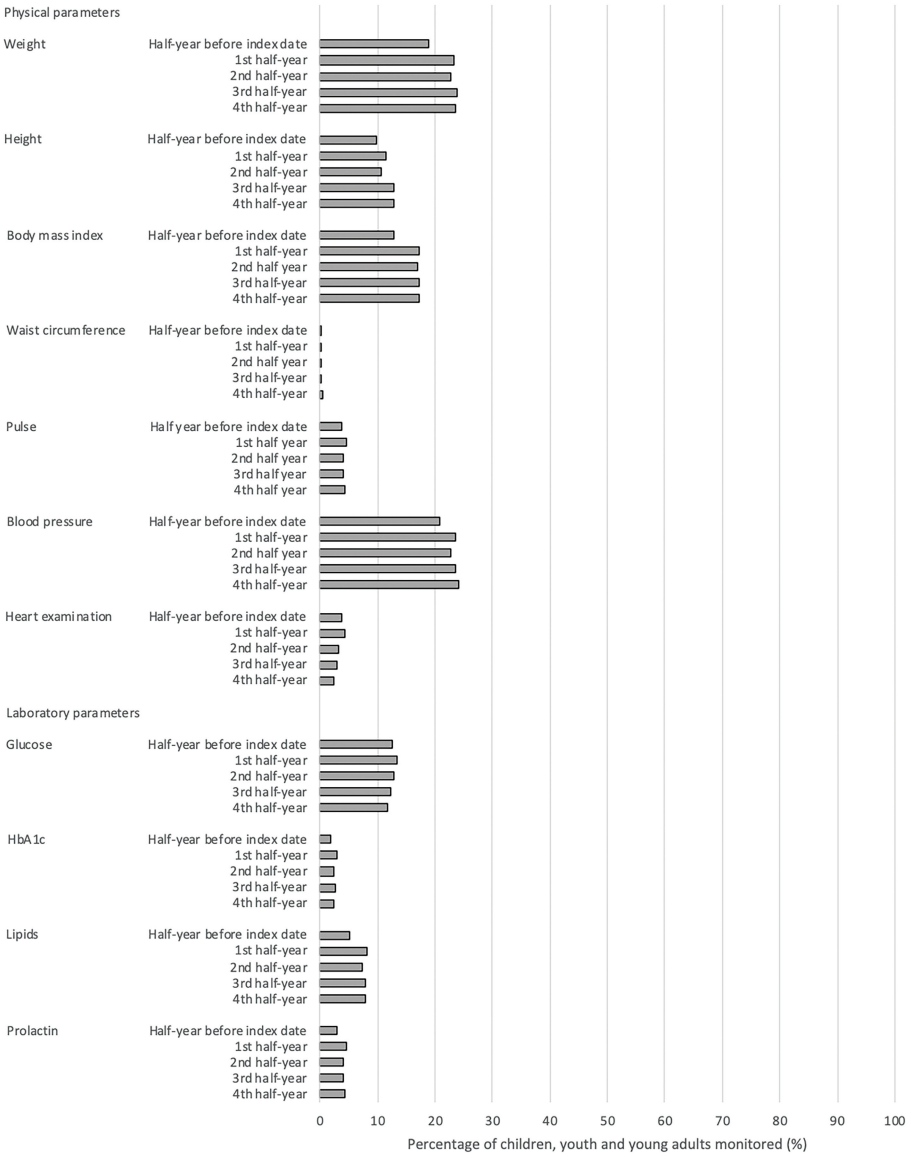
Index date: initial prescription of a second-generation antipsychotic drug in the CPRD database.
a. Total duration of follow-up (years): mean 1.6 and median 1.0.
b. Eighteen children, youth, and young adults were prescribed two types of second-generations antipsychotic drugs (n = 7,024).
c. Several children, youths, and young adults had more than one disorder and used multiple drugs (n >7,006). The disorders and drugs mentioned were a selection of those included in the CPRD database; children, youth, and young adults could also have other disorders and use other drugs not shown in this table.
CPRD, Clinical Practice Research Datalink.

Monitoring of physical and laboratory parameters

During each 6-month time frame, physical parameters were monitored in less than 25% of the youth and laboratory parameters in less than 15% (Figure 1). Although monitoring frequencies were low across all parameters, the physical parameters monitored most frequently in youth during the first half year that they were prescribed an SGA were blood pressure (n = 1,656; 23.6%) and weight (n = 1,640; 23.4%), and the laboratory parameters monitored most frequently were glucose (n = 937; 13.4%) and lipids (n = 565; 8.1%). Least frequently monitored parameters during the first half year were waist circumference (n = 13; 0.2%) and HbA1c (n = 205; 2.9%).

The duration of usage differed between youth (mean 1.6 years and median 1.0 year; Table 1), but no prominent differences were observed in monitoring frequencies during the first half year an SGA was prescribed when comparing youth who were prescribed an SGA for <12, 12 - 24, and ≥24 months.

Figure 1. Monitoring of adverse drug reaction-related parameters in children, youth, and young adults treated with second-generation antipsychotic drugs prescribed by general practitioners.



Total number of children, youth, and young adults: half year before the index date and 1st half year n = 7,006; 2nd half year n = 4,178; 3rd half year n=2,770; 4th half year n = 1,979.

Sex and age

Most parameters were monitored relatively more often in females compared with males during the first half year they were prescribed an SGA (Table 2); regardless, all parameters were monitored in less than 35% of the females. For example, BMI and blood pressure were monitored relatively more often in females than in males (24.5% vs. 12.7%: RR [95% CI] = 1.9 [1.7 - 2.1] and 33.6% vs. 17.5%: RR [95% CI] = 1.9 [1.8 - 2.1], respectively), as were glucose and prolactin (18.0% vs. 10.5%: RR [95% CI] = 1.7 [1.5 - 1.9] and 6.2% vs. 3.6%: RR [95% CI] = 1.7 [1.4 - 2.1], respectively).

Monitoring frequencies during the first half year differed across age categories (Table 2), but remained below 30% for all parameters. Height was monitored relatively more often in children 0 - 11 and 12 - 18 years old compared with those 19 - 24 years old (16.2% vs. 8.7%: RR [95% CI] = 1.9 [1.5 - 2.3] and 14.6% vs. 8.7%: RR [95% CI] = 1.7 [1.5 - 1.9], respectively). None of the children 0 - 11 years old were monitored for BMI; this was relatively most often monitored in those 19 - 24 years old (12 - 18/19 - 24 years old: 14.9% vs. 21.8%: RR [95% CI] = 0.7 [0.6 - 0.8]).

Table 2. Monitoring of adverse drug reaction-related parameters in children, youth, and young adults treated with second-generation antipsychotic drugs prescribed by general practitioners during the first half year: stratified by sex and age.

	Total	**Sex**			**Age (years old)**				
	n = 7,006	Male n = 4,330	Female n = 2,676	Female/male	0-11 n = 686	12-18 n = 2,539	19-24 n = 3,781	0-11/19-24	12-18/19-24
	%	%	%	RR [95%CI]	%	%	%	RR [95%CI]	RR [95%CI]
Physical parameters									
Weight	23.4	19.3	30.0	**1.6 [1.4-1.7]**	19.7	23.9	23.8	**0.8 [0.7-1.0]**	1.0 [0.9-1.1]
Height	11.6	11.6	11.5	1.0 [0.9-1.1]	16.2	14.6	8.7	**1.9 [1.5-2.3]**	**1.7 [1.5-1.9]**
Body mass index	17.2	12.7	24.5	**1.9 [1.7-2.1]**	0	14.9	21.8	-	**0.7 [0.6-0.8]**
Waist circumference	0.2	0.2	0.2	1.0 [0.3-3.1]	0	0.1	0.3	-	0.4 [0.1-1.6]
Pulse	4.5	3.6	6.0	**1.7 [1.4-2.1]**	4.7	4.7	4.3	1.1 [0.7-1.6]	1.1 [0.9-1.4]
Blood pressure	23.6	17.5	33.6	**1.9 [1.8-2.1]**	14.3	22.9	25.8	**0.6 [0.5-0.7]**	**0.9 [0.8-1.0]**
Heart examination	4.4	3.9	5.3	**1.4 [1.1-1.7]**	2.0	5.2	4.4	**0.5 [0.3-0.8]**	1.2 [1.0-1.5]
Laboratory parameters									
Glucose	13.4	10.5	18.0	**1.7 [1.5-1.9]**	6.0	13.8	14.4	**0.4 [0.3-0.6]**	1.0 [0.8-1.1]
HbA1c	2.9	2.3	4.0	**1.8 [1.3-2.3]**	0.4	3.0	3.4	**0.1 [0.0-0.4]**	0.9 [0.7-1.2]
Lipids	8.1	7.5	8.9	**1.2 [1.0-1.4]**	3.9	8.7	8.4	**0.5 [0.3-0.7]**	1.0 [0.9-1.2]
Prolactin	4.6	3.6	6.2	**1.7 [1.4-2.1]**	3.9	6.9	3.3	1.2 [0.8-1.8]	**2.1 [1.7-2.6]**

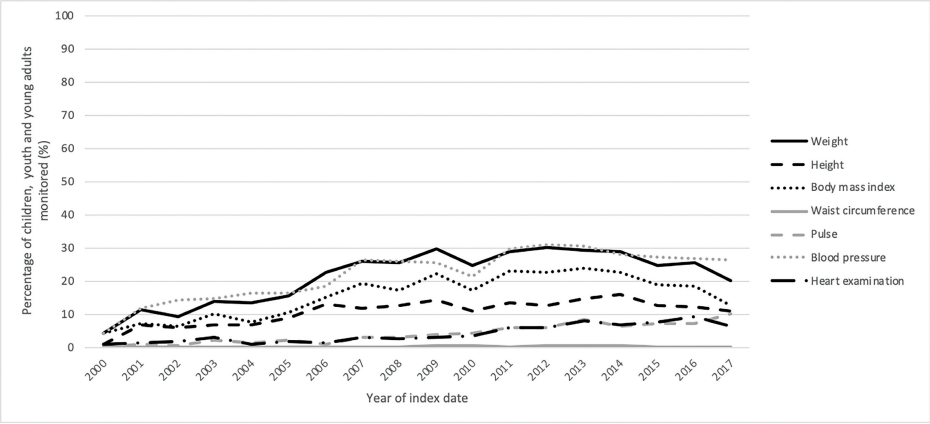
Bold: significant difference.
n, number of children, youth, and young adults; RR [95%CI], relative risk [95% confidence interval].

Calendar years

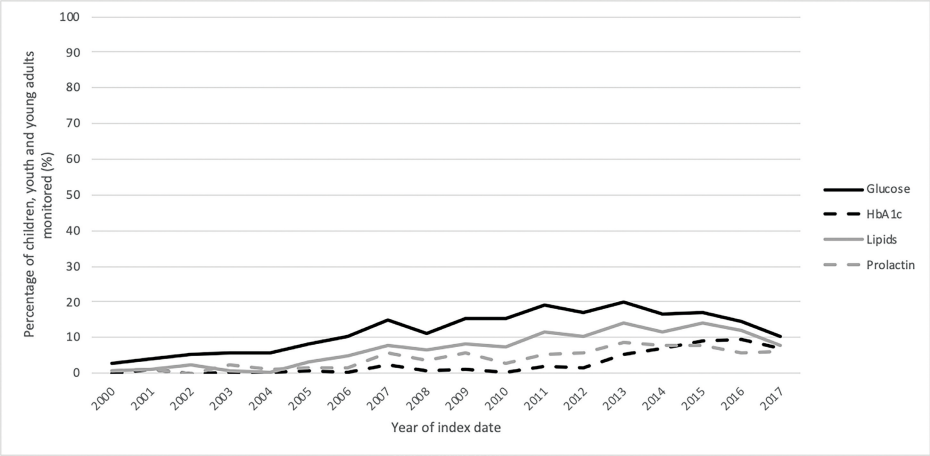
Monitoring frequencies of all parameters during the first half year that an SGA was prescribed increased compared with the year 2000, but in no year were the physical parameters monitored in more than 35% of the youth or laboratory parameters in more than 20% (Figure 2). Weight and blood pressure were monitored relatively most frequently when the year of the index date was 2012 (n = 157; 30.3% and n = 161; 31.0%, respectively). Glucose was monitored relatively most frequently when the year of the index date was 2013 (n = 113; 20.0%).

Figure 2. Monitoring of adverse drug reaction-related parameters in children, youth, and young adults treated with second-generation antipsychotic drugs prescribed by general practitioners during the first half year: stratified by calendar year.

2A. Monitoring of physical parameters



2B. Monitoring of laboratory parameters



DISCUSSION

Monitoring frequencies of ADR-related parameters were low in youth treated with an SGA prescribed by a GP. The physical parameters were monitored in less than 25% of the youth and laboratory parameters in less than 15% in the different 6-month time frames. There were no prominent changes in the percentages of youth monitored during the different 6-month time frames that they were prescribed an SGA. Although monitoring frequencies were low, females were monitored relatively more often than males, and there were some differences between age categories. Monitoring frequencies during the first half year that an SGA was prescribed increased after 2000, but did not exceed 35% in any year, and seemed to flatten over the years.

A study by Rettew et al.[27] indicated that metabolic monitoring is more likely to occur in children treated by psychiatrists compared with those treated by nonpsychiatrists, although a study by Wakefield et al.[28] revealed fewer differences in monitoring frequencies between psychiatrists and primary care providers. Previous studies have found different monitoring frequencies in youth, but the present findings—that these frequencies are low—are consistent.[16–20] A study by Rodday et al.[29] indicated that nearly all psychiatrists reported routinely monitoring height and weight in children, but waist circumference or an electrocardiogram was reported in less than a quarter of these children. Other studies also illustrated that monitoring frequencies for glucose were higher compared with lipids, but remained suboptimal.[18,19]

There were significant differences in monitoring frequencies indicated in this current study across sex and age categories. Previous studies have also shown that age may influence metabolic monitoring frequencies, as in these studies, older youth were monitored more often than younger children.[30,31] An explanation for this increase in monitoring of laboratory parameters with age could be the fear of needles as it has been shown that this fear is more common in younger children and decreases with increasing age.[32] Few previous studies have indicated the influence of sex on monitoring, but it seems that females were monitored relatively more often for laboratory parameters than males, as also shown in this current study.[18,31]

In the United Kingdom, the NICE guideline CG155 "Psychosis and schizophrenia in children and young people: recognition and management" provides recommendations on baseline investigations and monitoring for children and young people prescribed antipsychotic drugs.[23] This guideline was first published in 2013 and last updated in 2016 and recommends monitoring most parameters included in this study at baseline and every 6 months thereafter when an antipsychotic drug is prescribed. It advises that a heart examination (electrocardiogram) should be

performed only when there are risk factors present, including a personal or family history of cardiovascular disease. Looking into the results of this study, most youth were not monitored according to the recommendations of this guideline. Although the present study showed that monitoring frequencies have increased since 2000, no prominent increase was observed after introduction of the NICE guideline in 2013. Previous studies have also demonstrated that after the introduction of monitoring recommendations, warnings for ADRs or interventions, monitoring frequencies may increase, but remain inadequate.[33–37] One reason for the outcome of this current study could be that GPs were not aware or insufficiently informed about these new guideline recommendations. Therefore, although there are guidelines on how to monitor ADR-related parameters in youth treated with antipsychotic drugs, the majority of these youth remain unmonitored.

Medical record documentation of the medication and monitoring practices varies between health care professionals.[38] The quality of documentation can differ as well as the location within the medical record where the information is reported. For this study, monitoring of ADR-related parameters could also have been documented in different parts of the electronic medical records. When searching for monitoring practices within other parts of the medical records included in this study, it was not always clear whether monitoring was previously or currently performed, recommended, or just noted as a point of attention. Therefore, these data were not included in this study. Although this might have led to an underestimation of the monitoring frequencies, this would most likely not lead to considerable differences. Additionally, when data were recorded in different parts of the medical records, this could lead to unclear medical records, which would also deteriorate monitoring quality in daily clinical practice.

A strength of this study is that the data were drawn from the CPRD, a large anonymized GP database of high quality and representative of the whole population of the United Kingdom in sex, age, and ethnicity.[26] However, this study also has some limitations. Data on monitoring could have been missed if they were not recorded, such as when SGAs were iterated by a GP while the child was monitored by a psychiatrist and results not exchanged, or when data were recorded in an irretrievable part of the medical records, such as free text. Previously, laboratory results were recorded manually, probably resulting in recording only abnormal or confirmatory results. There is no clear date when GP practices switched to laboratory-linked electronic recording. These factors could lead to incomplete or unclear medical records and therefore underestimated monitoring frequencies. However, these missing data would also negatively influence monitoring quality in daily clinical practice. Finally, it could be that youth were deliberately not monitored, but the considerations and choices made concerning monitoring were not known.

CONCLUSION

Monitoring frequencies of ADR-related parameters in youth treated with SGAs prescribed by a GP were low. Monitoring in primary care should be improved for the early detection of ADRs and interventions where needed and to enable a better benefit-risk balance during antipsychotic drug therapy.

CLINICAL SIGNIFICANCE

Antipsychotic drugs can cause severe ADRs, which could have a great impact on the quality of life of youth. Therefore, monitoring of these ADRs is important. Nevertheless, this study showed that youth treated with SGAs were monitored infrequently for ADR-related physical and laboratory parameters. Future research should focus on identifying underlying barriers and facilitators for monitoring. These can be barriers involving the prescriber of an SGA, such as a lack of electronic facilitating systems, difficulty in collaborating with other health care professionals, lack of time, or insufficient knowledge about monitoring.[39–41] A previous study has shown that not all primary care providers were aware of the consensus guidelines.[41] Additionally, psychiatrists and primary care providers seem to have different preferences where monitoring should be performed, and also not all primary care providers share the same opinion, which makes collaboration even more important.[42] The NICE guideline "Autism spectrum disorder in under 19s: support and management" states that antipsychotic drug therapy should be started and monitored by a pediatrician or psychiatrist, and when it is transferred to primary care, the specialist should give clear guidance.[43] Barriers can also be related to the patient as parents can forget to obtain a laboratory test and may not see its importance or youth can refuse to take a test because of a fear of needles.[32]

Regarding facilitators, the use of an electronic medical record system can facilitate monitoring practices as this seems to improve the quality of clinical notes.[44] Including a reminder system to notify the health care professional about what should be monitored may further enhance monitoring practices. Additionally, shared decision-making may improve monitoring practices. Patients would like guidance and information on ADRs and monitoring of effects.[45,46] For young children, this information could be provided to their caregivers. Health care professionals involved in the antipsychotic drug therapy of youth, including GPs, psychiatrists, and pharmacists, have an important role in providing clear information and guidance. Explaining which effects could be expected and why monitoring is important may create more awareness and compliance to therapy, including monitoring. Investigating and prioritizing the barriers and facilitators could help improve the monitoring frequencies.

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Conflict of interest
Els van den Ban received a travel reimbursement from Medice to attend an international scientific convention on child and adolescent psychiatry (2017). She reports no financial interests or potential conflicts of interest. All other authors report no financial interests or potential conflicts of interest.

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SUPPLEMENTARY MATERIALS

Table S1. List of second generation antipsychotic drugs.

Drug substance name
Amisulpride
Aripiprazole
Clozapine
Lurasidone
Olanzapine
Paliperidone
Quetiapine
Risperidone
Sertindole
Zotepine

Table S2. Code lists of physical and laboratory parameters.

S2a. Laboratory parameters

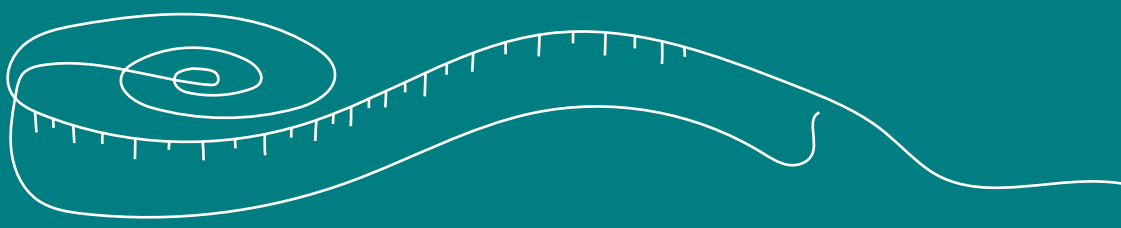
Enttype	Description	Filetype	Category
Glucose			
213	Blood glucose	Test	Biochemistry (Routine)
222	Glucose tolerance test	Test	Biochemistry (Routine)
274	Fasting glucose	Test	Biochemistry (Routine)
286	Urinalysis - Glucose	Test	Biochemistry (Routine)
430	Urine dipstick for glucose	Test	Biochemistry (Routine)
HbA1c			
275	HbA1c - diabetic control	Test	Biochemistry (Routine)
Lipids			
163	Serum cholesterol	Test	Biochemistry (Routine)
175	High density lipoprotein	Test	Biochemistry (Routine)
177	Low density lipoprotein	Test	Biochemistry (Routine)
202	Triglycerides	Test	Biochemistry (Routine)
206	Very low density lipoprotein	Test	Biochemistry (Routine)
214	Blood lipids	Test	Biochemistry (Routine)
338	HDL/LDL ratio	Test	Biochemistry (Routine)
Prolactin			
192	Prolactin level	Test	Biochemistry (Hormone)

HDL, high-density lipoprotein; LDL, low-density lipoprotein

S2b. Physical parameters

Enttype	Description	Filetype	Category
Blood pressure			
1	Blood pressure	Clinical	Examination Findings
392	Ambulatory blood pressure	Test	Diagnostic Tests
475	Target blood pressure	Clinical	Examination Findings
130	Pre - treatment BP	Clinical	Examination Findings
Pulse			
131	Pulse (CVS/BP)	Clinical	Examination Findings
Heart examination			
96	Heart examination	Clinical	Examination Findings
217	Electrocardiogram	Test	Diagnostic Tests
304	ECG exercise	Test	Diagnostic Tests
342	Echocardiogram	Test	Diagnostic Tests
379	ECG ambulatory	Test	Diagnostic Tests
Weight			
13	Weight	Clinical	Examination Findings
488	Weight loss	Clinical	Examination Findings
Height			
14	Height	Clinical	Examination Findings
Waist circumference			
476	Waist circumference	Clinical	Examination Findings
Body Mass Index			
	See 13. Weight (data3)		

BP, blood pressure; ECG, electrocardiogram



Chapter 4

Support during antipsychotic drug treatment

Chapter 4.1

Clarity and applicability of adverse drug reaction-related monitoring instructions in clinical practice guidelines for children and adolescents treated with antipsychotic drugs: a review of six clinical practice guidelines

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ABSTRACT

Objectives

Monitoring instructions related to adverse drug reactions (ADRs) are not always clearly described in clinical practice guidelines (CPGs) and not always easily applicable in daily clinical practice. The aim of this study was to assess the clarity of presentation and the applicability of ADR-related monitoring instructions in CPGs for children and adolescents treated with antipsychotic drugs.

Methods

Guidelines from different countries were selected, and monitoring instructions for 13 ADR-related parameters were assessed. To assess the clarity and the applicability of the sections concerning monitoring instructions in each CPG, the Appraisal of Guidelines for Research and Evaluation instrument was used. To assess the clarity and the applicability of the monitoring instructions for each ADR-related parameter, the Systematic Information for Monitoring score was used.

Results

Six CPGs were included. Overall, the presentation of the monitoring instructions in the different CPGs was clear; three CPGs scored >75%. All CPGs scored lower on applicability, as, for example, the barriers and facilitators were poorly described. The number of ADR-related parameters included in the CPGs varied between 8 and 13. Why and what to monitor was always described for each parameter. When to start monitoring was also often described (90.2%), but when to stop monitoring was less frequently described (37.4%).

Conclusion

The CPGs differed on the parameters that needed to be monitored. Overall, the monitoring instructions were clearly presented, but improvement in their applicability is required. By improving the monitoring instructions, CPGs can provide better guidance on monitoring ADRs in daily clinical practice.

INTRODUCTION

Antipsychotic drugs are widely prescribed on-label and off-label to children and adolescents (hereafter referred to as *children*) to treat psychiatric disorders and symptoms, including attention deficit/hyperactivity disorder, irritability related to autism, mood disorders, anxiety disorders and tics.[1,2] Evidence for the efficacy of antipsychotic drugs in this young and vulnerable population is not always available, while these drugs often cause bothersome, and sometimes severe, adverse drug reactions (ADRs).[3] ADRs associated with antipsychotic drug treatment in children include, for example, weight gain, abnormal blood glucose levels, tachycardia, gynecomastia, sexual dysfunction and movement disorders.[3–5] Adequate monitoring of individual children is important when considering treatment initiation, for the early identification of the development of ADRs and to evaluate and, when needed, adjust the antipsychotic drug treatment to balance efficacy and safety.

Multiple clinical practice guidelines (CPGs) worldwide provide guidance to healthcare professionals on how to monitor for ADRs in children treated with antipsychotic drugs.[6–11] These ADRs can be monitored through related parameters, including physical (weight, height, body mass index (BMI), waist circumference, blood pressure, pulse and electrocardiogram (ECG)), laboratory (glucose, glycated hemoglobin (HbA1c), lipids and prolactin), and observational (extrapyramidal and prolactin-related, for example, gynecomastia) parameters. There are differences between the CPGs in, for example, which ADR-related parameters should be monitored as well as the timing and frequency of monitoring. Regardless of these differences in the content of the instructions, all instructions aim to provide guidance to improve monitoring practices. Nevertheless, previous studies have shown that the monitoring of children treated with antipsychotic drugs is suboptimal and improved only marginally after the introduction of monitoring instructions provided in the CPGs.[12–14]

To enable the implementation of the monitoring instructions provided in the CPGs in daily clinical practice, first, the quality of the CPG is important, for example, the clarity of presentation. Second, each monitoring instruction included in the CPG has to be easily identifiable, clear, unambiguous and easy to apply. Each instruction should define why it is necessary to monitor, what to monitor, when to start, when to stop, how frequently to monitor, what to look for or what the critical values of the parameter are and how to respond to the monitoring results.[15] Clear and easily applicable CPGs could enhance monitoring in daily practice and thereby contribute to the safety of antipsychotic drug use in children. However, previous studies have shown that the monitoring instructions are not always clearly described in the CPGs and that the instructions are not always easily applicable in daily clinical practice.[16,17] This could lead to suboptimal monitoring frequencies and, consequently, to

unidentified ADRs. Therefore, the aim of this study was to assess the clarity of presentation and the applicability of ADR-related monitoring instructions in CPGs for children treated with antipsychotic drugs.

METHODS

Selection of the clinical practice guidelines

A search for CPGs that included ADR-related monitoring instructions for children treated with antipsychotic drugs was performed by using the literature database PubMed, the guideline-specific database of the Guidelines International Network (GIN) and the general search engine Google. The search terms for the CPGs were related to psychiatric symptoms and disorders, as well as antipsychotic drugs (online Supplemental Table 1).

The CPGs had to meet five criteria to be selected. First, the CPG had to be available in Dutch, English or German so that the reviewers could understand it. Second, the publication had to be titled as a guideline, or there had to be a statement to the effect that this publication was a guideline. When identified through Google, the CPG had to be linked to a website of a national or international association for child and adolescent psychiatry or a national healthcare organization. Third, the CPG had to include a section on antipsychotic drug treatment. Fourth, the CPG had to be focused on children (<18 years) or include at least one separate chapter on antipsychotic drug treatment in children. Finally, the full CPG had to be available in the public domain. The GIN database was not freely accessible and was, therefore, used to list published guidelines that were subsequently searched for on PubMed and Google.

A maximum of one CPG per country was included. When several CPGs emerged for the same country, those prioritized for this study were CPGs from child and adolescent psychiatry associations, CPGs for antipsychotic drug treatment instead of specific psychiatric disorders and CPGs with the most extensive sections in terms of follow-up and monitoring. There was one exception to the non-inclusion of more than one CPG for one country, namely when an organization had published more than one CPG on the treatment and follow-up of children prescribed antipsychotic drugs, and these CPGs referred to each other. The selected CPGs could have been revised, and the most recent versions were selected. To determine which CPGs should be included, three authors (LM, JWA and ERH) discussed all selected CPGs.

Selection of the monitoring instructions

A monitoring instruction was defined as an instruction on measuring a physical, laboratory, or observational ADR-related parameter before or during antipsychotic

drug treatment. In total, 13 ADR-related parameters were included, based on the cardiometabolic, endocrine, and extrapyramidal ADRs that can be caused by antipsychotic drugs.[13,14] The physical parameters included were weight, height, BMI, waist circumference, blood pressure, pulse and ECG. The laboratory parameters included were glucose, HbA1c, lipids and prolactin. The observational parameters included were extrapyramidal symptoms (eg, parkinsonism and akathisia) and prolactin-related symptoms (eg, gynecomastia, galactorrhea and sexual dysfunction).

All monitoring instructions for children treated with antipsychotic drugs were obtained from the included CPGs by reading them, and the sections concerning the treatment, risks, pretreatment advice and follow-up were carefully examined. In addition, terms relating to the ADR-related parameters, monitoring of the ADR-related parameters and drug safety were searched for in the entire CPGs. General instructions on psychotropic medications were excluded; antipsychotics had to be explicitly mentioned.

Clarity and applicability of the clinical practice guidelines

To assess the clarity of presentation and applicability of the complete sections concerning monitoring instructions in each CPG, eligible parts of the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument and its complement the AGREE-Recommendations Excellence (AGREE-REX) instrument were selected.[18,19] These instruments were designed by the AGREE Research Trust and are intended to help guideline users and developers to assess the methodological quality of guidelines.[18]

The two domains 4 and 5 of the AGREE-II instrument, with seven items in total, were considered eligible and relevant and therefore included for this study:

Clarity of presentation
- The recommendations are specific and unambiguous.
- The different options for management of the condition or health issue are clearly presented.
- Key recommendations are easily identifiable.

Applicability
- The guideline describes facilitators and barriers to its application.
- The guideline provides advice and/or tools on how the recommendations can be put into practice.
- The potential resource implications of applying the recommendations have been considered.
- The guideline presents monitoring and/or auditing criteria.

Furthermore, three domains of the AGREE-REX instrument, with seven items in total, were considered eligible and relevant and therefore included for this study:

Clinical applicability
- Evidence
- Applicability to target users
- Applicability to patients/populations

Values and preferences
- Values and preferences of target users
- Values and preferences of patients/populations

Implementability
- Purpose
- Local application and adoption

For each included CPG, all items were scored based on a seven-point scale, ranging from 1 (*strongly disagree*) to 7 (*strongly agree*) for the AGREE-II instrument, and 1 (*lowest quality*) to 7 (*highest quality*) for the AGREE-REX instrument.

Clarity and applicability of the monitoring instructions

To assess the clarity of presentation and applicability of the monitoring instructions for each ADR-related parameter, the Systematic Information for Monitoring (SIM) score was used.[15] With this score, the monitoring instructions were assessed based on six domains of information, namely: "what to monitor," "when to start monitoring," "when to stop monitoring," "how frequently to monitor," "what to look for/critical values of the parameter," and "how to respond." Each domain of information was allotted a score of either 0 (*not described/not clearly described*) or 1 (*clearly described*), resulting in a total score of between 0 and 6 (online Supplemental Table 2). The seventh domain, "why to monitor," was assessed separately. Four domains of the SIM score were considered to be essential for the clarity and applicability of a monitoring instruction, namely "what to monitor," "how frequently to monitor," "what to look for/critical values," and "how to respond."[15]

The AGREE and SIM scores were determined by two authors independently (JWA and LM) and discrepancies were discussed and resolved by consensus. Final inconsistencies were discussed with the other authors until consensus was reached.

Data analysis

To assess the clarity and applicability of the complete sections concerning monitoring instructions in each CPG, the AGREE scores were calculated. Final scores for each domain were calculated as a percentage of the maximum score, using the following formula:

$$\text{AGREE score (\%)} = \left[\frac{\text{obtained score} - \text{minimum possible score}}{\text{maximum possible score} - \text{minimum possible score}} \right] \times 100$$

Maximum possible score = 7 (strongly agree/higher quality) x number of items
Minimum possible score = 1 (strongly disagree/lower quality) x number of items

In addition, the monitoring instructions of the 13 ADR-related parameters (see section *Selection of the monitoring instructions*) were assessed separately. The number of monitoring instructions was calculated for each CPG, it was determined which instructions were most often missing, and whether the reason for the advice to monitor was included. To assess the clarity and applicability of each monitoring instruction, the SIM scores were calculated. The instructions that were considered to be clear and applicable were those with a SIM score ≥4 that included at least the four essential domains "what to monitor," "how frequently to monitor," "what to look for/critical value," and "how to respond."

RESULTS

In total, CPGs from six different countries that were retrieved through PubMed and Google searches were included after the selection criteria were applied (online Supplemental Table 3). Three CPGs from the Canadian Alliance for Monitoring Effectiveness and Safety of Antipsychotics in Children (CAMESA) were included, as the CAMESA had published three CPGs on monitoring and managing antipsychotic drug safety. These CPGs included one on monitoring the safety of second-generation antipsychotic drugs in children, one on managing metabolic complications and one on managing extrapyramidal side effects.[11,20,21] Hereafter, these three CAMESA guidelines will be referred to and assessed as being one CPG.

The years of publication of the most recent versions of the CPGs were between 2011 and 2020. The scope of four CPGs involved monitoring for the safety of antipsychotic drugs in children, and the scope of two CPGs was the treatment of schizophrenia, of which one was a guideline for adults but included a chapter regarding children.

Clinical practice guidelines

For the clarity of presentation according to the criteria of the AGREE II instrument, three CPGs scored >75% (Table 1). In most CPGs, the recommendations were specific and unambiguous (overall mean percentage: 75%), and the CPGs included easily identifiable tables listing the parameters that should be monitored (77.8%). However, the different options for the management of the condition or health issue were less

clearly presented in three CPGs (Women's and Children's Health Network (WCHN), National Institute for Health and Care Excellence (NICE) and American Academy of Child and Adolescent Psychiatry (AACAP); overall mean percentage: 50%). This item, on management of the condition, included responses to abnormal test results, which were lacking, unclear or incomplete in these CPGs. All CPGs scored lower on applicability compared with the clarity of presentation. Especially the item "potential resource implications of applying the recommendations" scored low (22.2%). This item included the cost information, which was extensively described in one CPG (NICE), but was lacking or insufficiently described in the other CPGs.

For the clinical applicability according to the criteria of the AGREE-REX instrument, all CPGs scored >65% (Table 2). The evidence was not always clearly described (63.9%), as, for example, the consistency of results, bias of the included studies, directness of the evidence and magnitude of the benefits and harms were not included or not completely described in all CPGs. Most CPGs scored low on the item concerning values and preferences of the target users and patients/populations (47.2% and 33.3%, respectively). The method by which the values and preferences were assessed in the CAMESA guideline was the most clearly and explicitly described, as the evidence had been discussed by experts and consensus reached and focus group sessions that involved families of children with mental health disorders had been held.[11] Regarding the implementability of the CPGs, all scored low on local application and adoption (22.2%), as, for example, the change required from current practice, relevant factors for successful dissemination and resource considerations needed to implement the recommendations were lacking or poorly described.

Table 1. AGREE II

Clinical Practice Guideline	Country	Clarity of presentation [a]			AGREE Score (%)	Applicability [b]				AGREE Score (%)
		4.1	4.2	4.3		5.1	5.2	5.3	5.4	
WCHN	Australia	6	3	5	61.1	3	6	1	5	45.8
CAMESA	Canada	6	7	6	88.9	5	6	3	6	66.7
DGPPN	Germany	6	5	6	77.8	2	2	2	4	25.0
Accare	The Netherlands	6	5	6	77.8	3	4	1	5	37.5
NICE	United Kingdom	4	1	6	44.4	2	2	6	3	37.5
AACAP	USA	5	3	5	55.6	2	2	1	3	16.7
Overall mean percentage		75.0	50.0	77.8		30.6	44.4	22.2	55.6	

Items AGREE-II:
a. 4.1 The recommendations are specific and unambiguous; 4.2 The different options for management of the condition or health issue are clearly presented; 4.3 Key recommendations are easily identifiable.
b. 5.1 The guideline describes facilitators and barriers to its application; 5.2 The guideline provides advice and/or tools on how the recommendations can be put into practice; 5.3 The potential resource implications of applying the recommendations have been considered; 5.4 The guideline presents monitoring and/or auditing criteria.
AACAP, American Academy of Child and Adolescent Psychiatry; AGREE, Appraisal of Guidelines for Research and Evaluation; CAMESA, The Canadian Alliance for Monitoring Effectiveness and Safety of Antipsychotics in Children; DGPPN, German Association for Psychiatry, Psychotherapy and Psychosomatics; NICE, National Institute for Health and Care Excellence; WCHN, Women's and Children's Health Network.

Table 2. AGREE-REX

		Clinical applicability [a]				Values and preferences [b]			Implementability [c]		
Clinical Practice Guideline	**Country**	**1.1**	**1.2**	**1.3**	**AGREE Score (%)**	**2.1**	**2.2**	**AGREE Score (%)**	**3.1**	**3.2**	**AGREE Score (%)**
WCHN	Australia	3	7	5	66.7	3	3	33.3	6	3	58.3
CAMESA	Canada	7	7	6	94.4	6	4	66.7	5	3	50.0
DGPPN	Germany	6	5	5	72.2	4	3	41.7	5	2	41.7
Accare	The Netherlands	3	6	6	66.7	3	3	33.3	5	1	33.3
NICE	United Kingdom	6	5	4	66.7	4	3	41.7	5	4	58.3
AACAP	USA	4	6	5	66.7	3	2	25.0	4	1	25.0
Overall mean percentage		63.9	83.3	69.4		47.2	33.3		66.7	22.2	

Items AGREE-REX:
a. 1.1 Evidence; 1.2 Applicability to target users; 1.3 Applicability to patients/populations.
b. 2.1 Values and preferences of target users; 2.2 Values and preferences of patients/populations.
c. 3.1 Purpose; 3.2 Local application and adoption.
AACAP, American Academy of Child and Adolescent Psychiatry; AGREE, Appraisal of Guidelines for Research and Evaluation; AGREE-REX, AGREE Recommendations Excellence; CAMESA, The Canadian Alliance for Monitoring Effectiveness and Safety of Antipsychotics in Children; DGPPN, German Association for Psychiatry, Psychotherapy and Psychosomatics; NICE, National Institute for Health and Care Excellence; WCHN, Women's and Children's Health Network.

Monitoring instructions

The number of ADR-related parameters included in the CPGs varied between 8 (Accare) and 13 (German Association for Psychiatry, Psychotherapy and Psychosomatics (DGPPN); Tables 3 and 4). Monitoring instructions for the parameters weight, BMI, blood glucose, lipids and prolactin were included in all CPGs (Table 3). Monitoring instructions for the physical parameters pulse and the performance of an ECG were most often missing, namely in 50% (WCHN, CAMESA and Accare) of the CPGs. Although the CAMESA guideline stated that the performance of an ECG was beyond the scope of the current guideline, a reference to an article with guidance on ECG monitoring was provided.[11] Monitoring instructions for waist circumference (WCHN and Accare) and HbA1c (WCHN and CAMESA) were missing in two of the CPGs, and monitoring instructions for height, blood pressure and the two observational parameters extrapyramidal symptoms (Accare) and prolactin-related symptoms (NICE) were missing in one CPG each. All CPGs described "why to monitor" by explaining the ADRs that could be caused by antipsychotic drugs.

Although the Accare guideline included the lowest number of monitoring instructions for ADR-related parameters (n = 8), all instructions that were included were considered to be clear and applicable, as they had a total SIM score of ≥4 and included the four essential domains (Table 4). For two CPGs (NICE and AACAP), none of the monitoring instructions were considered clear and applicable. The domain "what to monitor" was clearly described for all monitoring instructions in the different CPGs, whereas there were differences between the other domains. Overall, when to start monitoring was clearly described (90.2%). All CPGs advised healthcare professionals to start monitoring blood glucose and lipids at baseline, except for the Dutch guideline, which recommended to start monitoring only when there were risk factors present, for example, a high BMI or familial hypercholesterolemia. Four CPGs (WCHN, CAMESA, DGPPN and AACAP), did not clearly spell out when to stop monitoring, while the other two CPGs (Accare and NICE) advised monitoring for the duration of the treatment (overall mean percentage: 37.4%). Although the frequency of monitoring was described for most parameters (80.6%), these frequencies differed between the CPGs, as recommendations to monitor the laboratory parameters varied from half-yearly, yearly, an advice depending on the type of antipsychotic drug, to no advice on how to monitor beyond 1 year of antipsychotic drug treatment because of a lack of long-term evidence. Descriptions of what to look for or critical values (reference values) were missing for all laboratory parameters in three CPGs (DGPPN, NICE and AACAP; overall mean percentage: 68.7%), and how to respond if there were abnormalities in test results was not described for most parameters in these same three CPGs (58.0%).

Table 3. Scoring of monitoring instructions for each adverse drug reaction-related parameter.

	WCHN	**CAMESA**	**DGPPN**	**Accare**	**NICE**	**AACAP**
	Australia	Canada	Germany	The Netherlands	United Kingdom	USA
Physical parameters						
Weight	**5**	**5**	**5**	**6**	5	4
Height	4	4	1	**6**	5	-
Body mass index	**5**	**5**	4	**6**	5	5
Waist circumference	-	**5**	1	-	5	3
Blood pressure	**5**	**5**	3	-	5	3
Pulse	-	-	3	-	4	3
Electrocardiogram	-	-	**5**	-	4	4
Laboratory parameters						
Glucose	**5**	**5**	3	**6**	4	3
HbA1c	-	-	3	**6**	4	1
Lipids	**5**	**5**	3	**6**	4	2
Prolactin	**5**	4	4	**6**	4	1
Observational parameters						
Extrapyramidal symptoms	4	**5**	**5**	-	3	4
Prolactin-related symptoms	**5**	3	**5**	**6**	-	2

Maximum SIM score: 6. Including "what to monitor," "when to start monitoring," "when to stop monitoring," "how frequently to monitor," "what to look for/critical values of the parameter," and "how to respond."
Bold: SIM score ≥ 4 and including the four essential domains "what to monitor," "how frequently to monitor," "what to look for/critical value," and "how to respond."
- : Parameter not included in the clinical practice guideline.
AACAP, American Academy of Child and Adolescent Psychiatry; CAMESA, The Canadian Alliance for Monitoring Effectiveness and Safety of Antipsychotics in Children; DGPPN, German Association for Psychiatry, Psychotherapy and Psychosomatics; HbA1c, glycated hemoglobin; NICE, National Institute for Health and Care Excellence; SIM, Systematic Information for Monitoring; WCHN, Women's and Children's Health Network.

Table 4. Scoring of monitoring instructions for each clinical practice guideline.

Clinical practice guideline	Country	Number of instructions[a]	What to monitor (%)	When to start monitoring (%)	When to stop monitoring (%)	How frequently to monitor (%)	Critical value (%)	How to respond (%)	SIM Score ≥4[b] (%)
WCHN	Australia	9	100	100	0.0	100	100	77.8	77.8
CAMESA	Canada	10	100	90.0	0.0	90.0	90.0	90.0	70.0
DGPPN	Germany	13	100	84.6	7.7	76.9	38.5	38.5	30.8
Accare	The Netherlands	8	100	100	100	100	100	100	100
NICE	United Kingdom	12	100	100	100	91.7	41.7	0.0	0.0
AACAP	USA	12	100	66.7	16.7	25.0	41.7	41.7	0.0
Mean		10.7	100	90.2	37.4	80.6	68.7	58.0	46.4

a. Maximum number of parameters for which monitoring instructions were included: 13. Including the physical parameters weight, height, body mass index, waist circumference, blood pressure, pulse and electrocardiogram, the laboratory parameters glucose, glycated hemoglobin, lipids and prolactin and the observational parameters extrapyramidal symptoms and prolactin-related symptoms.
b. And including the four essential domains "what to monitor," "how frequently to monitor," "what to look for/critical value," and "how to respond."
AACAP, American Academy of Child and Adolescent Psychiatry; CAMESA, The Canadian Alliance for Monitoring Effectiveness and Safety of Antipsychotics in Children; DGPPN, German Association for Psychiatry, Psychotherapy and Psychosomatics; NICE, National Institute for Health and Care Excellence; SIM, Systematic Information for Monitoring; WCHN, Women's and Children's Health Network.

DISCUSSION

The clarity and applicability of ADR-related monitoring instructions in CPGs for children treated with antipsychotic drugs varied. Overall, the purpose and the presentation of the monitoring instructions in the CPGs were clear. However, the applicability could be improved, as, for example, the barriers, facilitators and cost implications were poorly described. In addition, recommendations on how to apply these instructions locally were missing or insufficiently described in all CPGs, as, for example, the changes required in current practice and relevant factors for successful dissemination were most often lacking. The applicability of the CPGs to healthcare professionals and children was more clearly presented than the description of the preferences of these two groups. Not only were there differences between the CPGs, but differences were also apparent in the completeness of ADR-related monitoring instructions of different parameters included in the same CPG. Although the number of parameters included varied between CPGs, all CPGs included instructions on weight, BMI, blood glucose, lipids and prolactin. Overall, what to monitor, when to start and the frequency of monitoring were most often described, while it was not always clear when to stop monitoring, what the critical values were or how to respond to abnormal test results. In particular, the applicability of the CPGs and of the individual monitoring instructions need to be improved for use in daily clinical practice.

Previous studies have also shown that monitoring instructions need improvement.[16,17,22–24] Brouwer et al. assessed the applicability of monitoring instructions in CPGs for elderly patients treated with antipsychotic drugs.[23] The number of instructions and the monitoring frequencies also differed between these guidelines. In addition, the critical values and how to respond to abnormal test results were insufficiently described, in line with several CPGs included in the current study, while the CPGs for elderly patients were clearer regarding when to stop monitoring. However, not only the monitoring instructions of antipsychotic drugs in CPGs need improvement. A study by Nederlof et al. regarding monitoring instructions for patients using lithium for the treatment of bipolar disorder and a study by Chiappini et al. regarding symptomatic management of fever in children indicated that the clarity of presentation was good in most CPGs, but the applicability could be improved, which is also in line with the results of the current study.[16,22] Moreover, the monitoring instructions in, for example, the summary of product characteristics also do not always provide adequate information, that is, easily applicable in daily clinical practice.[24]

The preferences of children, adolescents or their caregivers were poorly incorporated in the development process of most CPGs, or the extent to which the children, adolescents or their caregivers were involved remained unclear. Since CPGs

provide recommendations and instructions to optimize patient care, it is essential to consider the preferences of patients. Previous studies have shown that the involvement of patient representatives is important because this can, for example, influence the scope of the CPG, encourage the use of plain language, emphasize the importance in real life and lead to incorporation of patient-relevant topics and outcomes.[25,26] Via involvement of children, adolescents and their caregivers in the development process of monitoring instructions, the barriers to monitoring could also be discussed and possible solutions included in the CPGs. Barriers associated with children, adolescents or their caregivers could be a lack of knowledge, parents who resist or forget to obtain tests, or refusal by the child to take tests because of, for example, a fear of needles.[27]

The differences between the CPGs could be caused by several factors. First, the scope of the CPGs differed, as four CPGs focused on the safety of antipsychotic drug use in children, and two focused on schizophrenia. When the scope is broader and includes the overall therapy for a disorder, the focus on the monitoring instructions in the CPG could be less extensive, and this topic might be discussed in less detail. Second, five CPGs focused on children, while one CPG (DGPPN) focused on adults and included a section on children. Third, the year of last publication ranged from 2011 to 2020, and three CPGs had never been revised since the first publication. The quality of CPGs increased over time, which might result in higher quality in recent or frequently updated CPGs.[28] This increase in quality over time is not in line with the findings of the current study because, although the CAMESA guideline was published in 2011 and could improve in several domains, overall, this guideline scored high and could potentially be used as an example to improve other CPGs. Fourth, one CPG (Accare) was written for local use but published on a national website for child and adolescent psychiatry so that it could be used by other healthcare professionals.[6] By whom the CPG is developed could influence the clarity and applicability, as, for example, CPGs developed by international organizations seem to score high in those two domains, and these international organizations include a variety of expertise leading to a better understanding of, for example, implementation barriers.[28] Finally, several other factors influence the development and content of a CPG, for example, differences in clinical practice between countries.

After development and publication of a CPG, the CPG has to be disseminated, adopted and incorporated into daily clinical practice. A review by Fischer et al. provided information on barriers to guideline implementation.[29] The barriers described were related to the CPGs, for example, access to the guidelines, poor lay-out, lack of evidence, plausibility of recommendations, lack of applicability and complexity.[29] As shown in the current study, these barriers related to CPGs could also emerge in daily clinical practice when clear ADR-related monitoring instructions for children treated with antipsychotic drugs are required. Other barriers described include personal

factors related to the physicians' knowledge and attitude, for example, a lack of awareness, familiarity, skills or agreement with the guideline, or external factors, including a lack of resources or collaboration.[29] Before a healthcare professional can adhere to a CPG, he or she must be aware of this guideline. A study by McLaren et al. has shown that most child psychiatrists reported being aware of the CPGs for antipsychotic drug monitoring, while a study by Mangurian et al. has shown that a large proportion of the primary care providers seem to be unaware of the consensus guidelines.[27,30] Nevertheless, previous studies have demonstrated that monitoring rates were low and remained low after implementation of monitoring guidelines.[12,14] As far as we know, no studies have been conducted that evaluated whether (a) more clear and applicable CPGs lead to better CPG adherence, and (b) whether good adherence to such clinical guidelines for the monitoring of ADR-related parameters indeed leads to better clinical outcomes such as less ADRs or better recognition and management thereof. Since awareness might not be the largest barrier for all healthcare professionals, the barriers other than awareness should also be investigated, for example, barriers related to the adoption, implementation and applicability in daily clinical practice. However, several barriers do not stand alone but could be related to each other. For example, when CPGs are evidence based and include well-founded advice, healthcare professionals might be more likely to concur and adopt the monitoring instructions, and if a CPG is easy to follow and apply in daily clinical practice, adhering to the monitoring instructions will be less time consuming. Therefore, clear and easily applicable CPGs might also decrease other barriers to monitoring.

A strength of this study was that only those CPGs including ADR-related monitoring instructions for children treated with antipsychotic drugs were examined. In addition, the AGREE-instrument and SIM-scores were used to assess the content and quality of the monitoring instructions in the CPGs. A limitation is that we selected six CPGs based on language (Dutch, English, German) and public availability. However, our main goal was to assess clarity and applicability in some widely used CPGs and not to identify all nor the best CPGs. Furthermore, a limitation is the possible subjectivity in scoring these CPGs. However, the scoring of the CPGs and individual monitoring instructions was performed by two reviewers independently, and discrepancies were discussed and resolved by consensus. Information could have been missed, but that would have meant that it had been overlooked by two reviewers and might also not be clear for daily clinical practice. The summary of product characteristics (SmPCs) of approved drugs is another important source of information for prescribing and monitoring drugs.[24] We did not take these into account in the present study, since CPGs are more patient and treatment oriented and include relevant product-oriented information such as available from SmPCs. The applicability of monitoring instructions included in SmPCs is generally lower than that included in CPGs.[24]

CONCLUSION

The CPGs differed on the parameters that needed to be monitored and in the content of the monitoring instructions. Overall, the monitoring instructions in CPGs for children treated with antipsychotic drugs were clearly presented, while the applicability needed improvement. More information is required on how to put the recommendations into (local) practice, what the facilitators and barriers are and potential resource implications of applying these recommendations. Furthermore, the CPGs did not all clearly describe when to stop monitoring, what to look for or the critical values of the parameters and how to respond to abnormal test results. By improving the monitoring instructions, CPGs can provide better guidance so that monitoring practices can improve in daily clinical practice, and ADRs can be identified in a timely fashion.

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Conflict of interest
None declared.

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SUPPLEMENTARY MATERIALS

Supplemental Table 1. Search strategies

PubMed **Search: September 2019**	
MeSH-terms applicable to this study	child; adolescent; antipsychotic agents; schizophrenia; mental disorders; autism spectrum disorder; drug-related side effects and adverse reactions; drug monitoring; patient safety; aftercare; practice guideline [publication type]
Examples of MeSH-term combinations used	((“Antipsychotic Agents”[Mesh]) AND “Child”[Mesh]) AND “Adolescent”[Mesh]
	(“Antipsychotic Agents”[Mesh] AND “Child”[Mesh] AND “Adolescent”[Mesh]) guidelines
	((“Antipsychotic Agents”[Mesh]) AND “Child”[Mesh]) AND “Adolescent”[Mesh] clinical practice guidelines
	(“Antipsychotic Agents”[Mesh] AND “Child”[Mesh] AND “Adolescent”[Mesh]) (“guideline”[ptyp])
Search terms used (differently combined)	Antipsychotic agents; second generation antipsychotics; child; adolescent; (clinical practice) guideline; mental disorder; schizophrenia; monitoring; adverse effects
Guideline International Network **Search: September 2019**	
Search terms used	Schizophrenia; autism spectrum disorder(s); ASD; autism; pervasive developmental disorder; Asperger; disruptive behavior disorder(s); bipolar disorder(s); attention deficit hyperactivity disorder(s); ADHD; antipsychotic(s); antipsychotic agent(s); antipsychotic drug(s)
Google **Search: September – October 2019**	
Search terms used	The search terms were translated into the language of the country concerned, e.g. when the Dutch guideline was sought: “Vereniging kinder- en jeugdpsychiatrie Nederland” was entered into Google.
	Association of child- and adolescent psychiatry + name of the country concerned
	Clinical practice guidelines of antipsychotics in children and adolescents + name of the country concerned
	Clinical practice guidelines of schizophrenia/autism spectrum disorder in children and adolescents + name of the country concerned
	Guidelines on monitoring adverse effects of antipsychotics in children and adolescents + name of the country concerned
	Monitoring safety of antipsychotics in children and adolescents + name of the country concerned

Supplemental Table 2. Systematic Information for Monitoring (SIM) score.

Domain	Example	Score
What to monitor	Blood levels	0
	Blood glucose levels	1
When to start monitoring	Measure weight at regular intervals during treatment	0
	Measure weight before starting antipsychotic medication	1
When to stop monitoring	Monitor blood pressure annually	0
	Monitor blood pressure throughout treatment	1
How frequently to monitor	Monitor blood lipids at regular intervals during treatment	0
	Monitor blood lipids at baseline, at 3 months, then yearly	1
What to look for/critical value	Weight	0
	Plot weight on a growth chart	1
	Blood prolactin level	0
	Blood prolactin level girls <500 mE/L	1
How to respond	Monitoring is advised.	0
	When abnormal blood glucose levels, consultation with or referral to a pediatrician is advised.	1
	When symptoms of elevated prolactin do develop, treatment considerations should include: decrease dosing, switching to a different antipsychotic drug, or medication discontinuation.	1

Reference
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Supplemental Table 3. Characteristics of included clinical practice guidelines.

Country	Clinical practice guideline	Year of publication (year of last approval/review)	Publishing society	Abbreviation
Australia	Clinical procedure. Antipsychotic medication – Monitoring adverse effects when prescribed for children / adolescents	2015 (2020)	Women's and Children's Health Network	WCHN
Canada	- Evidence-based recommendations for monitoring safety of second-generation antipsychotics in children and youth - Management recommendations for metabolic complications associated with second-generation antipsychotic use in children and youth - Treatment recommendations for extrapyramidal side effects associated with second-generation antipsychotic use in children and youth	2011	The Canadian Alliance for Monitoring Effectiveness and Safety of Antipsychotics in Children guideline group	CAMESA
Germany	S3-Leitlinie Schizophrenie	2019	Deutsche Gesellschaft für Psychiatrie und Psychotherapie, Psychosomatik und Nervenheilkunde e. V.	DGPPN
The Netherlands	Formularium Psychofarmaca Accare. Monitoring op metabole en endocriene bijwerkingen van antipsychotica	2009 (2014)	Accare Kinder- en Jeugdpsychiatrie	Accare
United Kingdom	Clinical guideline. Psychosis and schizophrenia in children and young people: recognition and management (CG155)	2013 (2016)	National Institute for Health and Care Excellence	NICE
United States of America	Practice parameter for the use of atypical antipsychotic medications in children and adolescents	2011	American Academy of Child and Adolescent Psychiatry	AACAP

Chapter 4.2

Support from healthcare professionals during antipsychotic drug treatment: experiences of adolescents with a tic disorder

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Els van den Ban

Preliminary results

ABSTRACT

Objective

It is important to provide optimal support to children and adolescents with a tic disorder treated with antipsychotic drugs. Although antipsychotic drugs can be effective in reducing tic severity in children and adolescents, these drugs are also associated with distressing and severe adverse drug reactions (ADRs) that can have physical, emotional, and social impacts. The aim of this study was to assess the experiences of adolescents with a tic disorder regarding the support received from healthcare professionals during antipsychotic drug treatment.

Methods

Adolescents aged 12-18 years with a tic disorder who had been treated with an antipsychotic drug for at least three months were included. They were recruited through a Dutch organization for patients with Tourette syndrome. Semi-structured interviews were conducted, based on a predefined topic list. The interviews were conducted online and video-recorded. The recordings were transcribed, and data was analyzed using inductive thematic analysis.

Results

Thus far, two adolescents have been interviewed. Their experiences regarding support from healthcare professionals differed. One adolescent was rather satisfied with the support received, while the other one did not receive sufficient support to form a clear picture of what to expect and how to cope with the ADRs that occurred. Nevertheless, their need for support was quite similar, as they both expressed, for example, a need for personal contact with their healthcare professionals and to be involved in the decision making.

Conclusion

Although more interviews are needed to gain insight into how adolescents with a tic disorder treated with antipsychotic drugs can be optimally supported and to be able to draw conclusions, these preliminary results show that support should be personalized.

INTRODUCTION

Tics are common in children and often have an early onset, between the ages of 4–6 years old.[1] Tics peak in severity between 10–12 years of age, and, thereafter, there is often a decline in severity.[1] The diagnosis of a tic disorder depends on the age of onset, the duration of the tic symptoms, the presence of vocal and/or motor tics, and the absence of a known cause.[1] Treatment of tic disorders consists of psychoeducation and behavioral therapy, but can also include medication, for example, antipsychotic drugs.[2–4] Although antipsychotic drugs can be effective in reducing tic severity and frequency, these drugs can also cause distressing and severe adverse drug reactions (ADRs) that can have physical, emotional, and social impacts.[2,5–7] Therefore, monitoring for efficacy and possible ADRs and providing support to children and adolescents on antipsychotic drug treatment is important in optimizing the balance between the benefits and the potential harm.[8]

ADRs associated with antipsychotic drugs include, for example, weight gain, abnormal blood glucose levels, abnormal blood lipid profile, hypertension, gynecomastia, sexual dysfunction, sedation, and movement disorders.[5,6] The ADRs can be monitored through related parameters, including physical parameters (e.g., weight, body mass index [BMI], and blood pressure), laboratory parameters (e.g., blood glucose, lipids, and prolactin), and observational parameters (e.g., movement disorders, galactorrhea, and gynecomastia). Monitoring can also be done by simply asking the child or adolescent whether they have experienced ADRs, for example, sedation and headache. The parameters that should be monitored and how frequently this should be done are described in the clinical practice guidelines and the Summary of Product Characteristics (SmPC).[9–11]

Children and adolescents are continuously developing, not only physically but also emotionally, socially, and cognitively. The ADRs that might occur during antipsychotic drug treatment can have a significant physical impact, which can differ in frequency and severity in children compared to adults, as, for example, the extent of weight gain seems to be greater in the younger population.[12] However, ADRs do not only have a physical impact but might also have emotional consequences. For example, weight gain or gynecomastia can have a great impact on self-image and self-confidence during puberty. Monitoring can also have emotional consequences and influence the child or adolescents' quality of life, considering a possible fear of needles and the constant reminder of their tic disorder and the antipsychotic drug treatment. In addition, the social environment of children and adolescents is important, and it is meaningful to consider how they cope with the use of antipsychotic drugs in relation to friends or classmates. Feelings of shame regarding the occurrence of ADRs, the use of antipsychotic drugs, and stigmatization may influence their young lives.[13] All

of this can potentially affect their motivation and adherence to the antipsychotic drug therapy.

During the process of growth and development, a child progresses from being totally dependent on their parents or caregivers to becoming more and more independent. Adolescents are reaching an age where they are likely to manage their own medication, ask more questions, and self-monitor their therapy. In addition, in the Netherlands, children from the age of 12 years have to consent to their therapy, according to the provisions of Medical Treatment Contracts Act (WGBO). Therefore, not only is optimal information to the parents or caregivers important, but the children and adolescents also have to be provided with the most optimal support at their level of knowledge and tailored to their individual need. Previous studies have shown that there is a need for improvement in the support of patients treated with psychotropic drugs and that the content, communication, and organization of support are essential.[14–16] To gain more insight into how children and adolescents can be optimally supported, we have to ask them about and discuss with them their needs and preferences.[17] Their opinions, concerns, expectations, experiences, and advice are indispensable to enable healthcare professionals to provide optimal support. Therefore, the aim of this study was to assess the experiences of adolescents with a tic disorder regarding the support received from healthcare professionals during antipsychotic drug treatment.

METHODS

Design

A qualitative approach was used. Semi-structured interviews were conducted to assess adolescents' experiences regarding support during antipsychotic drug treatment.

Setting and study population

This qualitative study included adolescents with a tic disorder treated with antipsychotic drugs who were recruited through Stichting Gilles de la Tourette, which is a Dutch not-for-profit organization for patients with Tourette syndrome, their family and friends, healthcare professionals, teachers, researchers, and other interested parties.[18] The organization aims to raise awareness of Tourette syndrome and to improve the quality of life and social position of children and adults with Tourette syndrome by, for example, providing information, organizing peer support, and stimulating research into Tourette syndrome.[18]

For this study, adolescents were eligible for inclusion if they were aged between 12 and 18 years, had used an antipsychotic drug (ATC code N05A, excluding lithium

[N05AN01]) for more than three months for the treatment of a tic disorder at the time of the interview, and spoke Dutch. The total number of participants included depended on when data saturation was achieved. Data saturation was achieved when no new information was uncovered in further interviews, and additional interviews would not change the current results and conclusions.

Approval for this study was obtained from the institutional review board of the Department of Pharmaceutical Sciences of Utrecht University (reference number UPF2103) and the advisory board of Stichting Gilles de la Tourette. The Medical Research Ethics Committee (MREC) Utrecht confirmed that the Medical Research Involving Human Subjects Act (WMO) did not apply to this study (reference number 21/118).

Interviews

A call for participation was posted on the website of Stichting Gilles de la Tourette (https://tourette.nl/), in their newsletter, on their WhatsApp group for adolescents, and on their social media accounts, including Facebook, Instagram, and Twitter. Adolescents who wanted to participate received an email that included one information folder for themselves and one for their parent(s) or caregiver(s). This folder included more detailed information about the study and the adolescents or parents' rights. If an adolescent was younger than 16 years, they needed consent by a parent or caregiver to participate in this study. However, if an adolescent was aged 16 years or older, this consent was not required. The adolescents also received an informed consent form for themselves and, depending on their age, for their parent(s) or caregiver(s). In addition, they received a short questionnaire, that included questions regarding their age, contact information, which antipsychotic drug they were currently using, whether they had used another type of antipsychotic drug before and how many, for how long they had used antipsychotic drugs, whether they used other drugs, and whether they wanted a summary of the study results after the study was completed. After signing the informed consent and completing the questionnaire, the adolescents were registered to participate in the study. They received a letter with information about the study to inform their healthcare professionals. Before the interviews, they were contacted by telephone to allow them to ask any remaining questions, explain what they wanted to do if they should experience an escalation in the tics during the interview, since exciting or stressful events can worsen tics, and to set a date for the interview.

One semi-structured interview was conducted with each adolescent to collect the data. With a semi-structured interview, there is a topic list and a set of predetermined questions, but there are also questions that emerge during the interview. This allows the interviewer to ask more in-depth questions about certain topics that arise during the interview. The predefined topics for the interviews were 1) the support

the adolescents received regarding the potential development of ADRs caused by the antipsychotic drugs, 2) the support the adolescents received regarding the monitoring of these ADRs, 3) the support the adolescents received regarding the positive effects of the antipsychotic drugs, 4) the adolescents' involvement in their own antipsychotic drug therapy, and 5) their experiences, preferences, needs, and suggestions for improvement concerning these topics. The topic list and the predetermined questions were compiled from the content of a counseling interview used when dispensing a drug for the first time and through consultation with three child and adolescent psychiatrists, two adolescents, and two experts.

The objective of the study was explained again before the interview, as well as the right of the participant to not answer a question or to stop at any time. There was an opening question intended to relax the participant. At the end of the interview, a summary was provided to crosscheck the perspectives of the interviewee. The total duration of each interview was 30–45 minutes. The day after the interview, the participant was contacted by telephone to ask about his or her experience of the interview and whether there were any remaining comments or questions the participant would like to add. The participants subsequently received a gift card.

The interviews were conducted online by two researchers (LM and DT); they were not acquainted with the participants prior to the study. The first author (LM) is a researcher and pharmacist, and she asked the questions and led the interviews. The second author (DT) took notes, ensured that all topics were discussed, and asked additional questions. To gain more knowledge of and experience with conducting interviews, the first author participated in a course related to qualitative research in healthcare.

Data analysis

The interviews were conducted online using Microsoft Teams (version 1.4) and were video-recorded. The recordings were transcribed and anonymized by one of the researchers (DT), and the transcriptions were verified by the second researcher (LM). The analysis of the transcriptions was performed with NVivo (version 12). Data was analyzed using inductive thematic analysis. First, the data was coded, whereby sections of the text were labeled with codes that briefly described their content. Second, patterns were identified among these codes and arranged into themes. The analysis was conducted by two researchers (LM and DT), independently. Discrepancies were discussed and resolved by consensus, after which a final list, including codes and overarching themes, was composed. During this study, we alternated the interviews and analyses to determine whether data saturation had been achieved.

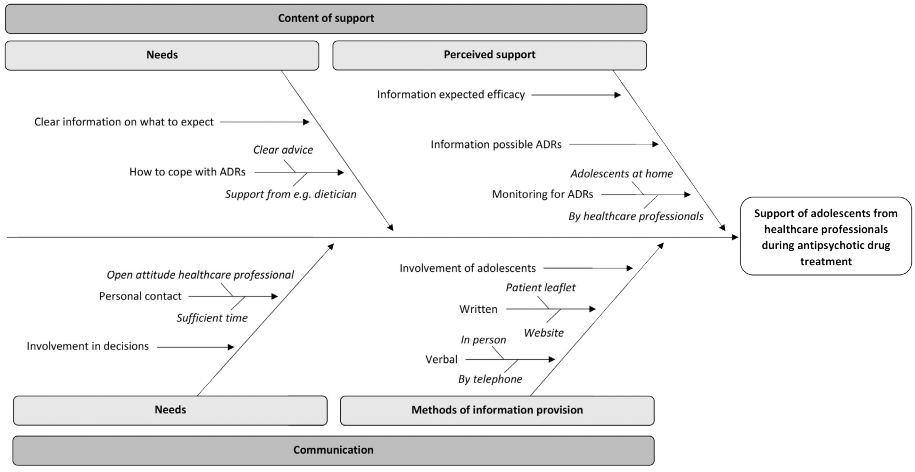
RESULTS

Thus far, two adolescents have been interviewed. The results below are the preliminary results.

Two adolescents who had used an antipsychotic drug for more than three months at the time of the interview were included in this study. Both were female and aged between 16 and 18 years. One was treated with aripiprazole at the time of the interview and the other with risperidone.

The analysis revealed two overarching themes, namely the content of the support and the communication (Figure 1). The support related to content was divided into the needs of the adolescents and their perception of the support received regarding the efficacy of the prescribed antipsychotic drug, the potential ADRs, and the monitoring of the ADRs. The communication was divided into the needs of the adolescents and the methods used to impart information.

Figure 1. Ishikawa diagram outlining the themes regarding the support of adolescents received from healthcare professionals during antipsychotic drug treatment.



ADR, adverse drug reaction.

Content of support

Needs

The adolescents expressed that they preferred clear information on the efficacy and ADRs of the drugs and what to expect from it. Monitoring for ADRs was also appreciated and, in addition, they mentioned a need for support in coping with ADRs if these occurred.

"Discuss the adverse effects carefully, and keep a close eye on what changes in that person during the first few, well, months, I think. And maybe also give a few tips when they mention adverse effects, like, maybe then you can do this, maybe then you can do that." [101]

Perceived support: efficacy and adverse drug reactions

Both adolescents received information from their psychiatrists about the expected effects of the prescribed antipsychotic drug, including the indication for the drug and the possible ADRs. Both adolescents mentioned that the drug really helped to control their tics, and one expressed that she was glad that there was a drug that could help her.

"Basically, I was already happy that there was something that would help me. So I thought, well, if that helps, then it is actually already fine. As long as the adverse effect don't get too intense. And that didn't really happen. I do suffer from it, from the adverse effects, but it is not… I think I would have more trouble with myself when I didn't take medication than I do now." [101]

One adolescent was satisfied with the information she received from the psychiatrist, and, regarding the ADRs, she said that she mostly remembered the information about weight gain and headache. She collected the drug from the pharmacy herself the first time it was prescribed and there she received verbal as well as written information. She felt that all the information was clear.

"Well, that they explain everything very clearly. That they give you the information you need and that you, well let's say, deserve." [102]

When the antipsychotic drug treatment was first initiated, she had different questions about the drug compared to later on during treatment.

"Does it cause many adverse effects, does it make me ill, will I be more vulnerable for things? Yes, those were the questions I had at that time." [102]

While on the antipsychotic drug, she wondered whether she would ever be able to stop using it and how to taper off.

Although the other adolescent mentioned that she had received information about a few ADRs from the psychiatrist, she was not clear on what to expect. Before she started using the antipsychotic drug, she read the patient information leaflet and discussed it with her parents. She did not collect the drug from the pharmacy herself the first time it was prescribed.

Perceived support: monitoring for adverse drug reactions

The adolescents were both monitored for weight, height, and blood pressure. They were also asked about the occurrence of ADRs. One adolescent had a blood sample drawn before she started using the antipsychotic drug and during the treatment to monitor, for example, cholesterol and glucose. Although monitoring was mostly done by the healthcare professionals, the adolescents also monitored themselves for ADRs. For example, one had a blood glucose meter at home and the other mentioned that she watched her own weight. One adolescent indicated that she knew that monitoring had to be done frequently, but that she did not receive comprehensive information on this issue. However, she mentioned that she was satisfied with the fact that she was being monitored for ADRs.

"I like it that I get the monitoring results quite fast. Most often, I receive them within one week and I really like that. Then you also know where you stand." [102]

Both adolescents had experienced several ADRs and mentioned the impact on their daily lives. For example, they both struggled with weight gain, and one was often tired. They expressed that they were not completely satisfied with the support that they received on how to cope with the ADRs. One adolescent was about to consult a dietician, but she would have preferred to have visited a dietician earlier during antipsychotic drug treatment. However, she did not understand what they meant regarding the weight gain earlier in the treatment.

"In the beginning, I found it difficult to deal with this, because I was always checked on my weight when I went to the doctor, but now I learn to deal with it more. Now I also understand why they say it and maybe that was it. Earlier, I did not get it, so I found it hard to understand, but now I get it why they say things and I want to do something about it." [102]

The other adolescent mentioned that, in addition to monitoring, she would have preferred more guidance and advice on how to cope with the ADRs she experienced as a result of the antipsychotic drug therapy.

"I go to the psychiatrist every, well, few months, I think, for a check-up. And then it is mostly just measuring blood pressure, weight, and height. And then it is like: okay, that is it. And, for example, what I suffer from, and then I say for example… For example, last time I gained more weight and then they say: okay, maybe you have to start moving a bit more. And that's it you know. And then I think: okay, but I also just have other problems. But well…" [101]

Communication

Needs

The adolescents expressed a need for personal contact with their healthcare professionals, including enough time during their appointments and feeling that they could ask their healthcare professional anything.

"Maybe just a real conversation, instead of just checking quickly." [101]

They also mentioned that they want to be involved in conversations and decisions making about their therapy.

Methods of information provision

Both adolescents felt that their healthcare professionals were rather busy, and one adolescent felt that she had limited time during appointments with her healthcare professional. She mentioned that it would be better if more time was allocated for an appointment.

"Mostly, I have the feeling it is quite short. Like they have a time limit. You need to get out quickly, you know. It would be better if they just took more time for everything, I think." [101]

Nevertheless, both adolescents felt that their healthcare professionals listened to them and that they could ask them all their questions. In addition, they both felt that they had a choice and were involved in the decisions on whether to start or continue their antipsychotic drug therapy.

"I think they are very open. So, when you have something on your mind, you can just tell them." [101]

"I liked it that I could co-decide what I was going to take, and that I could share my opinion and choices." [102]

Most information was provided verbally, and one adolescent was guided to a website with information on what patients with tics experienced with their medication.

They had also both received written information from the pharmacy, for example, the patient information leaflet. One adolescent pointed out that, although she preferred to receive the information verbally because it was easier to understand, she also liked the written information to remind her of what she had been told. The other adolescent did not have a preference for the manner in which information is imparted, provided that there was personal contact.

One adolescent estimated that she had an appointment with her psychiatrist once every four months. The other adolescent only visited the psychiatrist during the first three months of her antipsychotic drug therapy, after which they had contact via telephone and she only visited the psychiatrist physically when, for example, changes in her medication were required. Although she liked the telephonic contact, she mentioned that it was better to visit the psychiatrist physically initially, because, at that point, she had more questions about the antipsychotic drug.

"I like it that she calls often to see if everything is going well. Because imagine that I didn't tell them, and she would call and something is wrong, then you can just tell her." [102]

DISCUSSION

Only preliminary results of this current study can be shown. More interviews are required to gain insight into how adolescents treated with antipsychotic drugs can be optimally supported and to be able to draw conclusions. The experiences of the two adolescents interviewed differed regarding the support received from healthcare professionals during their antipsychotic drug treatment. While one adolescent was rather satisfied with the support she received, the other one did not receive enough support to form a clear picture of what to expect and how to cope with the ADRs that occurred. Nevertheless, their need for support was rather similar. They both expressed a need for clear information about what to expect, advice on how to cope with ADRs, and personal contact with their healthcare professional to ask questions and discuss their therapy. They both mentioned that they felt that they could ask their healthcare professionals anything and that they were involved in the decision making.

The preliminary results show that personalized support by healthcare professionals is desired, and that there is room for improvement of this support. Previous studies have also shown that there is a need for more support from healthcare professionals.[13–16,19] Murphy et al. indicated that there is a gap in young people's knowledge about antipsychotic drug therapy and in support from, for example, health services, family, or school.[13] Lake et al. studied the views of parents of adolescents and young adults with autism spectrum disorder regarding their

children's psychotropic drug use, and found that not all parents were satisfied with the way their children were monitored.[16] Nederlof et al. assessed the guidance from physicians and pharmacists for adults using antidepressants.[14] They found that there is a need for information throughout the treatment and for clear advice during decisional moments, for example, what to expect regarding the positive effects and the possible ADRs. The results from previous studies are in line with the preliminary results of the current study, as these adolescents also expressed a need for knowledge about the antipsychotic drugs prescribed and for support during the antipsychotic drug treatment regarding, for example, what to expect from the treatment and how to cope with the ADRs.

Although the experiences of the adolescents included in this study differed, they both appreciated personal contact with their healthcare professionals and being involved in the choices regarding their therapy. Shared decision making seems to be important during antipsychotic drug treatment. Shared decision making means that both the healthcare professional and the adolescent are involved in any decisions.[20] They both bring their own expertise, as the healthcare professional brings expertise in the possible antipsychotic drug treatment, including the potential benefits and risks, and the adolescent brings expertise related to their values, needs, and preferences.[20] Without listening to the voice of the adolescents, healthcare professionals might miss essential information necessary to make clinical decisions. For the adolescents, it could lead to a better understanding of their own therapy, including why it is important to be monitored and feeling more comfortable with the use of their antipsychotic drug, and, subsequently, it could induce greater acceptance of the antipsychotic drug therapy and improved motivation and compliance. To achieve this, personalized support can be meaningful, whereby the content, amount, and route of information provision is tailored to the adolescent.

Two adolescents have been interviewed thus far and data saturation has not been achieved. More adolescents have to be recruited and interviewed to achieve data saturation and to be able to draw conclusions. In addition, by recruiting more adolescents, we can not only assess their experiences but we might also be able to provide suggestions for improvement regarding the support they receive from healthcare professionals during antipsychotic drug treatment. A call for participation through Stichting Gilles de la Tourette not did garner enough response from possible participants for this study. To include more participants, we want to recruit adolescents through Karakter, a large Dutch academic child and adolescent psychiatry organization that operates in 12 locations and offers clinical and outpatient therapy to children up to the age of 18 years old from across the Netherlands. This study will be continued.

CONCLUSION

Although more interviews are needed to gain insight into how adolescents with a tic disorder treated with antipsychotic drugs can be optimally supported and to be able to draw conclusions, these preliminary results show that support should be personalized.

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Conflict of interest
The authors declare no conflicts of interest.

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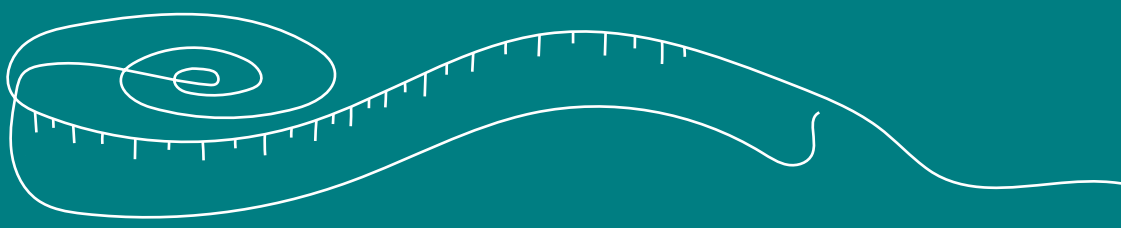

Chapter 5

General discussion

Children and adolescents can have several psychiatric symptoms and disorders, including behavioral disorders, irritability associated with autism, eating disorders, tic disorders, and attention-deficit/hyperactivity disorder. Treatment generally consists of a combination of psychoeducation, behavioral and psychosocial interventions, and psychotherapy, and can also include pharmacotherapy, for example, with antipsychotic drugs.[1,2] In 2019, the prevalence of antipsychotic drug use among Dutch children and adolescents up to the age of 19 years was 8.5 per 1,000, and risperidone was the most frequently prescribed drug.[3] Several steps are required according to the 6-step method of the World Health Organization's (WHO) Guide to Good Prescribing to choose the optimal treatment and to decide whether pharmacotherapy is indicated.[4,5] These steps include 1) defining the problem, 2) specifying the therapeutic objective, 3) reviewing available treatment options and evidence from sources like clinical practice guidelines (CPGs), 4) selecting the treatment that is suitable for the individual child or adolescent, 5) providing clear information and instructions, and 6) monitoring and evaluating the treatment and making adjustments when necessary. However, these steps are not always that straightforward. In psychiatry, it can be challenging to follow these steps, as the steps can overlap, and sometimes it can be one step forward and two steps back. In addition, it is not always clear what the most suitable treatment is, and providing clear information and instructions to a child with, for example, an autism spectrum disorder can be challenging. When choosing a treatment, consultation with the child or adolescent and the parents or caregivers about the treatment and shared decision making is indispensable at every step.

When an antipsychotic drug is prescribed for a child or adolescent, monitoring is essential to evaluate the positive as well as the negative effects that may occur, with consideration of the therapeutic objective. While less is known about the effects and appropriate dosages of antipsychotic drugs for children compared with adults, these drugs are prescribed on-label but also mostly off-label to this young and vulnerable population.[6,7] It is known that antipsychotic drugs can cause severe adverse drug reactions (ADRs), including weight gain, abnormal blood glucose levels, gynecomastia, and extrapyramidal effects.[8–11] However, the occurrence and severity of ADRs can differ between adults and children, as children are at greater risk of severe weight gain and to experience somnolence.[12,13] ADRs not only have a physical impact on the child or adolescent, but can also have a great emotional and social impact. For example, weight gain or gynecomastia often have a great impact on self-confidence during puberty. Adequate monitoring should aim at detecting ADRs at an early stage to adjust the therapy as required and to achieve a safe antipsychotic drug treatment.

Advice and instructions on monitoring for ADRs in children and adolescents treated with antipsychotic drugs are described in CPGs as well as in the Summary of Product

Characteristics (SmPC) of the specific antipsychotic drugs. For implementation in daily clinical practice, these instructions have to be clear and easily applicable.[14] However, there is no clear evidence available regarding which ADR-related parameters have to be monitored to ensure drug safety and the frequency of monitoring. This makes it difficult to provide clear monitoring instructions for daily practice.

When a child or adolescent has to start treatment with antipsychotic drugs, this will most likely have a great impact on not only their lives but also affect the lives of their parents or caregivers, siblings, classmates, and friends.[15,16] During the entire course of antipsychotic drug treatment, healthcare professionals have to provide support to the children and adolescents as well as their parents and caregivers. The support has to be tailored to their level of knowledge, individual needs, and preferences. Personalized support for children and adolescents will help them to understand what to expect and why and how to take the drug, and it may promote self-management to increase adherence, achieve the maximum positive effect, and reduce the burden of using an antipsychotic drug.

The aim of this thesis was to assess the daily clinical practice of monitoring for ADRs of antipsychotic drugs in children and adolescents, including the facilitators for and barriers to monitoring.

First, the need for monitoring was assessed. The frequencies of spontaneously reported ADRs in children and adolescents treated with antipsychotic drugs worldwide were determined by assessing data from VigiBase. VigiBase is the WHO's global database that includes spontaneous reports of suspected ADRs from, for example, healthcare professionals and patients.[17] A wide spectrum of reported ADRs (n = 45,201), for which an antipsychotic drug was the suspected culprit, were found when searching for children and adolescents. Most frequently reported were ADRs related to extrapyramidal symptoms (14.7%), breast disorders or blood prolactin level changes (4.7%), and cardiac arrhythmias (4.6%). There were differences in reported ADRs between age classes, but the differences in reporting from healthcare professionals and from consumers (e.g., the children, adolescents, parents, and caregivers) were more striking. It may be that consumers mainly report those ADRs that influence the children's quality of life and constitute a burden to them, for example, weight gain, whereas health care professionals may not always regard these ADRs as posing a significant health risk and report on more objectively examined ADRs, for example, hematopoietic cytopenia.[16]

Second, the frequency of monitoring for ADR-related parameters in children and adolescents treated with antipsychotic drugs by healthcare professionals was assessed. By distributing questionnaires to prescribers at a conference, examining

electronic medical records in psychiatric outpatient clinics, and searching a database of medical records of general practices, we gained insight into the monitoring frequencies in daily clinical practice. We searched for the monitoring frequencies of physical (e.g., weight and blood pressure) and laboratory (e.g., blood glucose and lipids) parameters. Monitoring frequencies varied, and especially the monitoring frequencies of laboratory parameters were low. Monitoring frequencies appeared to be greater when healthcare professionals self-reported their monitoring practices as opposed to the data accessed in the medical records or in an existing database. This could be due to social or professional desirability response bias. We also searched the electronic medical records of psychiatric outpatient clinics for information regarding monitoring. However, reasons why monitoring was not performed were rarely recorded.

Third, we examined the support available to healthcare professionals in clinical practice guidelines (CPGs). The clarity of presentation and the applicability of ADR-related monitoring instructions for children and adolescents treated with antipsychotic drugs in CPGs were assessed. Six CPGs from different countries were included. Although all CPGs advised monitoring of some parameters, for example, weight and blood glucose, the CPGs also differed on which parameters should be monitored and in the content of monitoring instructions. What to monitor, when to start, and the frequency of monitoring were most often described, while it was not always clear when to stop monitoring, what the critical values were, or how to respond to abnormal test results. Although monitoring instructions were mainly clearly presented, the applicability of the CPGs can be improved, as, for example, barriers, facilitators, and how to apply the CPGs in daily clinical practice were often missing or poorly described.

Finally, adolescents' experiences of support from healthcare professionals during antipsychotic drug treatment was assessed. Thus far, two adolescents with a tic disorder have been interviewed. Their needs for support were quite similar, as they both wanted advice on how to cope with ADRs and personal contact with their healthcare professional. However, their experiences regarding the support provided differed. More interviews are necessary to gain insight into how adolescents with a tic disorder can be optimally supported, but these preliminary results already show that support should be personalized.

In this general discussion, these findings are discussed in a broader context. I discuss what is required for optimal monitoring and how this can be achieved in clinical practice. In addition, I provide suggestions for further research and education.

Achieving optimal monitoring

Monitoring is essential to safely prescribe an antipsychotic drug to a child or adolescent. However, these children and adolescents should not be monitored just for the sake of monitoring, but monitoring should add value and increase drug safety. Optimal monitoring should be pursued. In this chapter, I discuss six topics that are related to achieving optimal monitoring in daily clinical practice. These topics are 1) the child or adolescent at the center of the treatment, 2) responsibility for monitoring, 3) knowledge of healthcare professionals, 4) documentation and exchanging information, 5) relevant adverse drug reaction-related parameters, and 6) clear and easily applicable clinical practice guidelines.

1. The child or adolescent at the center of the treatment

During antipsychotic drug treatment, including monitoring, the child or adolescent should be at the center of the treatment. Children and adolescents who require treatment with antipsychotic drugs should be able to live their lives without having concerns about their drugs, including monitoring for and experiencing ADRs. They are growing up and developing physically, emotionally, and socially. They are in the process of discovering their own identities on their journey to adulthood. If a child or adolescent has to start treatment with antipsychotic drugs during this process, it will most likely have a great impact on their life.[15] The aim of antipsychotic drug treatment is to control the symptoms a child or adolescent exhibits, for example, tics or aggression associated with autism spectrum disorder, and to improve their quality of life. However, the ADRs that may occur during drug treatment in addition to the desired positive effect as well as monitoring for ADRs can be a burden and change a young person's life, not only physically but also emotionally. For example, as shown in Chapter 4.2, weight gain caused by antipsychotic drug use can have a great impact on self-esteem and can negatively affect the quality of life. In addition, monitoring of body weight can also be a burden, as the child or adolescent will be frequently confronted with the (potential) weight gain and the risk of developing diabetes mellitus. However, individual children and adolescents differ regarding their values, preferences, and experiences. One child may suffer because of gaining weight, while another may be pleased with the positive effect of the antipsychotic drug and is able to cope with the weight gain. It is important that the individual child or adolescent remains at the center of the therapy by consideration of their individual values, preferences, and needs, to improve their quality of life and decrease the burden of the antipsychotic drug treatment, including the burden of monitoring.

When the child or adolescent is at the center of the therapy, support for antipsychotic drug monitoring is essential. This support needs to be tailored to their level and needs. If they are unaware of why monitoring is important, they may be less

willing to have a blood sample taken to measure blood glucose levels or to stand on a scale. In addition, understanding their antipsychotic drug treatment may help them to cope with using the drugs and with the effects in their daily lives, not only for themselves but also, for example, towards friends and classmates. Previous studies have shown that patients require better support, and that the content of the support and communication are important aspects.[18–20] In one of our studies, in Chapter 4.2, the adolescents treated with an antipsychotic drug expressed a need for clear information about what to expect, advice on how to cope with ADRs, and personal contact with their healthcare professional to ask questions and discuss their therapy.

What is required to achieve this?

To ensure that the child or adolescent is at the center of the therapy, they need to be involved in the decisions regarding the antipsychotic drug treatment. Each child or adolescent should be supported by their healthcare professionals, and the support should be tailored to their age, level of knowledge, individual needs, and preferences. Since not all children will understand the antipsychotic drug treatment, their parents or caregivers must also be involved. To gain more insight into the support an individual child or adolescent and their parents or caregivers require regarding the antipsychotic drug treatment and what they think is important concerning the therapy, we have to ask about and discuss with them their needs and preferences.[21,22] Therefore, shared decision making is indispensable to ensure that the child or adolescent is at the center of the therapy, to achieve optimal monitoring, and to pursue the success of the antipsychotic drug treatment.[23] With shared decision making, on the one hand, healthcare professionals can learn about the preferences, values, needs, and experiences of the children and adolescents. On the other hand, children and adolescents can receive tailored information from the healthcare professionals to understand their treatment, and the therapeutic objectives and treatment, including the importance of monitoring, can be discussed. To succeed in shared decision making, a good relationship, trust, accessibility, and communication are important.

An inherent part of shared decision making is carefully listening to the child or adolescent. Healthcare professionals need to listen to the child or adolescent as well as to the parents or caregivers to learn which ADRs they experience as a burden in daily life and what monitoring practices have a greater impact. The child or adolescent may find some ADRs that occur to be more important or distressing than a healthcare professional would.[16] In one of our studies, in Chapter 2.1, we found that children and adolescents report different ADRs related to antipsychotic drugs than what healthcare professionals report. While healthcare professionals reported more objectively examined ADRs, for example, hematopoietic cytopenia,

children, adolescents, their parents, and caregivers reported the ADRs that are a burden to the child or adolescent, for example, weight gain or breast disorders. In daily life, an increase in weight or gynecomastia can be a visible burden to the child or adolescent and will directly influence their quality of life, while a change in blood levels cannot be noticed by their friends at school. Especially for children who are developing physically, emotionally, and socially, the occurrence of a visible ADR may have a great impact. It is important that healthcare professionals should keep this in mind and pay special attention to the ADRs that have the greatest impact on the child or adolescent, even though they may not always be the most clinically relevant ADRs.

2. Responsibility for monitoring

It is not always clear whose responsibility it is to monitor a child or adolescent treated with an antipsychotic drug.[24,25] When a child or adolescent is prescribed an antipsychotic drug, several healthcare professionals are, have been, or will be involved during the therapy. In one of our studies, in Chapter 3.2, we searched medical records of children and adolescents treated with antipsychotic drugs in psychiatric outpatient clinics. Multiple healthcare professionals were mentioned in relation to the therapy in the medical records, including a child and adolescent psychiatrist, pediatrician, and general practitioner. The monitoring practices of general practitioners were further examined in Chapter 3.3. The antipsychotic drug is most often initiated by a child and adolescent psychiatrist. A general practitioner may have been previously involved in identifying a problem and referring the child or adolescent to the child and adolescent psychiatrist or may continue prescribing the antipsychotic drug in collaboration with the child and adolescent psychiatrist. Before an antipsychotic drug is prescribed, the problem has to be defined more precisely and another therapy has often been tried, for example, psychotherapy. There may be a social worker or child psychologist involved during this earlier process as well as during the antipsychotic drug treatment. When an antipsychotic drug is prescribed, it needs to be collected from the pharmacy. The pharmacist will check the prescription, including the type of drug, dose, and duration of use, and provide information to the child or adolescent and the parents or caregivers about how to use the drug and what to expect. During the drug treatment, a child and adolescent psychiatrist can refer the child or adolescent to a pediatrician, cardiologist, or general practitioner to monitor for somatic ADRs, which should be reported in the medical record or treatment plan. A child or adolescent can also be referred to a dietician to prevent weight gain, to advise on weight loss, or to discuss a healthy diet. When a child or adolescent needs to provide a blood sample to monitor blood glucose, lipids, or prolactin, a laboratory becomes involved in the process and has to provide accurate measurements in a timely manner. In addition, a child or adolescent can relocate during therapy and switch to a different general

practitioner or psychiatrist. Eventually, when an adolescent turns 18 years old, the psychiatric care will be transferred to adult psychiatry, and different healthcare professionals will be involved.

Because multiple healthcare professionals are involved before and during antipsychotic drug treatment, it is important that it is clear whose responsibility it is to monitor, to inform other healthcare professionals about the monitoring and the monitoring findings, to act on the findings when these are abnormal, and to continue monitoring. First, it should be clear who monitors for which ADRs, otherwise there may be a lack of monitoring and, thereby, of drug safety, or monitoring may be performed too often. For example, a general practitioner may weigh a child or adolescent and measure their blood pressure and the following day the child or adolescent visits a child and adolescent psychiatrist who is unaware of this monitoring and may repeat it. This may not sound like a significant problem, but it is time consuming, requires additional administrative work, and, more importantly, can be a burden to the child or adolescent, which is simply unnecessary. Second, the involved healthcare professionals should be aware of the most recent monitoring outcomes and current therapy, which means that not only the monitoring but also the exchanging of the outcomes are important. For example, when blood glucose is tested in a laboratory or an ECG is done by the pediatrician, the child and adolescent psychiatrist should be notified of the test results to evaluate the antipsychotic drug treatment and adjust it if necessary. Moreover, the pharmacist should be well-acquainted with all medication, how it is used, actually occurring ADRs, and changes in therapy to be able to provide appropriate information and monitor drug safety. One of our studies, in Chapter 3.2, showed that monitoring outcomes are not always exchanged, as some children treated with an antipsychotic drug in a psychiatric outpatient clinic were referred to another healthcare professional to monitor for somatic ADRs, but the monitoring outcomes were not noted in the medical records of the psychiatric clinic. Third, when the monitoring outcomes are known, it has to be clear whose responsibility it is to evaluate the current therapy and adjust as required. Thereafter, the monitoring of the child or adolescent needs to continue, as monitoring is a never-ending necessity during antipsychotic drug treatment.

What is required to achieve this?

When multiple healthcare professionals focus on a part of the "antipsychotic drug treatment puzzle" of a child or adolescent and no one oversees the overall picture, it can lead to mistakes and suboptimal treatment, including suboptimal monitoring. Previous studies have shown that, in daily clinical practice, it is not always clear who is responsible for the progress and monitoring of the treatment.[24,26] Therefore, there should ideally be one coordinating practitioner who has complete overview and is knowledgeable about antipsychotic drug treatment, including monitoring

for ADRs, and can ensure that the most optimal treatment is provided. The coordinating practitioner should be agreed upon and made known to the other healthcare professionals involved, the child or adolescent, and the parents or caregivers from the start of the antipsychotic drug treatment. There are several healthcare professionals who can potentially perform this role, including the general practitioner, the child and adolescent psychiatrist, and the pharmacist. The general practitioner usually has an overview of the children and adolescents' health, including mental as well as physical health, and can monitor the somatic parameters during the antipsychotic drug treatment. However, a general practitioner may not have the experience and required knowledge of antipsychotic drug treatment, including the effects, the monitoring, and the follow-up, as they may have a small number of these children and adolescents registered in their practice. The child and adolescent psychiatrist defines the problem, considers the available treatment options suitable for the individual child or adolescent, and initiates the antipsychotic drug. The child and adolescent psychiatrist has the necessary knowledge and experience of the effects and monitoring of the ADRs related to antipsychotic drug use in children and adolescents. However, other aspects of the children or adolescents' health may not be known to them. The pharmacist has a complete overview of the drug therapy of a child or adolescent, including drugs for psychiatric as well as somatic symptoms or diseases, is familiar with the evidence and the effects, and can advise on the required monitoring. The pharmacist also provides information about the drugs to the children or adolescents and parents or caregivers and enquires about the possible occurrence of ADRs. However, the pharmacist has no insight into any additional therapy and is not always aware of the reasons why the drugs are prescribed. This makes it difficult to obtain a complete overview of the therapy of a child or adolescent treated with an antipsychotic drug. In daily clinical practice, the child and adolescent psychiatrist should ideally be the coordinating practitioner, as they are familiar with antipsychotic drug treatment in children and adolescents, initiate and prescribe the antipsychotic drug, and adjust the therapy as required.

Although being the coordinating practitioner may be time consuming, monitoring practices can be outsourced. As previously mentioned, monitoring of the somatic parameters can also be done by the general practitioner or the pediatrician. Monitoring of possible ADRs can also be done by someone working in the psychiatric clinic other than the child and adolescent psychiatrist. In the Netherlands, there are nurse practitioners who work at general practices (*praktijkondersteuner huisarts; POH)*, supporting the general practitioners. This may also be the case in psychiatric clinics. Nurse practitioners can monitor the children and adolescents for ADRs, interpretate test results, and guide the child or adolescent during antipsychotic drug treatment. Where and by whom ADRs should be monitored can be discussed with the children or adolescents and parents or caregivers, to learn about their

preferences. Monitoring outcomes and follow-up of the treatment can be discussed with, for example, a pediatrician, when the child and adolescent psychiatrist is not sure what the clinical consequences are of somatic ADRs. In addition, the child or adolescent can be referred to another healthcare professional, such as a dietician or general practitioner, for the treatment of or guidance on an ADR. With multiple healthcare professionals involved, processing all information and including it in the medical records is time consuming, but this can be outsourced to an administrative assistant. There should be agreement on which monitoring outcomes have to be communicated to the coordinating practitioner to retain an overview and what is expected from the coordinating practitioner regarding the antipsychotic drug treatment and communication to other healthcare professionals. Although the coordinating practitioner should have an overview of the antipsychotic drug treatment and ensure that the most optimal antipsychotic drug treatment is provided, every healthcare professional involved still has a responsibility regarding the care provided and the sharing of the monitoring outcomes timeously. The provision of optimal antipsychotic drug treatment, including monitoring for ADRs, is a shared responsibility.

In addition to the healthcare professionals, the child or adolescent, as well as their parents or caregivers, also need to be involved in the monitoring for ADRs. Adolescents like to be involved in their therapy, as shown in Chapter 4.2. The children or adolescents and their parents or caregivers may have better insight into the development of ADRs since they have to deal with taking the drug and cope with the effects every day. In addition, monitoring at home may reduce the burden, and the monitoring outcomes may differ, depending on the place where it is performed. For example, blood pressure can be higher when measured at a general practice than when measured at home. When monitoring at home is preferred and agreed upon through shared decision making, clear information is essential. Hereby the child or adolescent and parents or caregivers understand the antipsychotic drug effects, why monitoring is important, and what parameters they need to monitor. It needs to be agreed upon what is monitored at home, how and how frequently it should be done, and how and where to report the outcomes. For example, they need information about how to properly measure blood pressure or blood glucose levels at home but also about how frequently they have to be weighed. It needs to be discussed whether the child or adolescent is capable to do this by themselves, with or without the help of a parent or caregiver. Subsequently, they need to inform the healthcare professionals about the outcomes and discuss the follow-up of the monitoring and the treatment. This can be done by telephone or email, but it may also be possible to report the monitoring outcomes, the antipsychotic drug effects experienced, and related questions directly in the electronic medical records. By involving the children and adolescents in the monitoring practices, they will become

partly responsible for and more involved in their own therapy, which can possibly increase awareness as well as drug safety.

3. Knowledge of healthcare professionals

Healthcare professionals involved in the antipsychotic drug treatment of children and adolescents should be aware of the effects and the required monitoring. Previous studies have shown that limited knowledge about ADRs and on how to conduct measurements and interpreted the results can be barriers for monitoring.[25,27] Especially when prescribing an antipsychotic drug to a child or adolescent, it is essential to understand why and when monitoring is advised, consider the individual child or adolescent, be able to find reliable information regarding monitoring, tailor monitoring practices to daily life, understand the monitoring outcomes, know what to do when an outcome is abnormal, and be able to deviate from the guidelines in a substantiated manner.

In addition to knowledge of monitoring the children and adolescents treated with antipsychotic drugs, healthcare professionals also need optimal communication skills to support these children and adolescents, provide tailored information, and make shared decisions. A previous study has shown that there were gaps in the knowledge of youth about antipsychotic drugs.[15] There can be a lack in information provision, but it may also be that not all information provided will be easily remembered by the child, adolescent, parents, or caregivers. The way information is provided is important, as shown in Chapter 4.2.

What is required to achieve this?

Education about treatment of children and adolescents with an antipsychotic drug is essential to become acquainted with the effects of antipsychotic drugs and monitoring for ADRs and to acquire communication skills. Education on content and training of communication skills already starts at university for child and adolescent psychiatrists, general practitioners, and pharmacists in the Netherlands. During the years after graduation, refresher courses are offered to keep pace with new developments in antipsychotic drug therapy. The levels of knowledge of and experience with monitoring for ADRs related to antipsychotic drugs will differ between professionals, as each profession has a specific focus. For example, a child and adolescent psychiatrist will know the effects of antipsychotic drugs, as they are mostly in close contact with the child or adolescent in daily clinical practice, while a pharmacist will know more about the evidence regarding effects and can support the psychiatrist, child or adolescent, and parents or caregivers, especially in relation to the (safe) use of the antipsychotic drug.

Knowledge of and experience with the effects of antipsychotic drugs on children and adolescents does not only differ between professions but also between individual healthcare professionals. For example, not every community pharmacist will have the same number of children and adolescents who use an antipsychotic drug registered at their pharmacy. Therefore, it is not realistic to assume that every pharmacist will know everything about antipsychotic drug treatment for children and adolescents, including monitoring, and will be able to keep pace with the latest developments. There are community pharmacists in the Netherlands with an interest, education, and expertise in a specific area (*kaderapothekers)*, and child and adolescent psychiatry should be included as possible specific area. In addition, there are community or hospital pharmacists who provide medication to psychiatric clinics and, therefore, should have knowledge of the effects of antipsychotic drugs on children and adolescents and be able to advise other healthcare professionals. Every individual healthcare professional has to be aware of their own boundaries regarding their knowledge and should at least know where to find reliable information when needed. There is information available online; in the Netherlands, professionals can find information on a website for child and adolescent psychiatry (www.kenniscentrum-kjp.nl) or on a website that provides information about drugs, including dosages, warnings, and ADRs (www.kinderformularium.nl). In addition, when searching for information, collaboration is essential. It should be possible for a pharmacist to consult a colleague who has experience and knowledge, but also to enable healthcare professionals to ask other healthcare professionals for advice. Knowledge of each other's expertise and who to ask for or where to find reliable information is essential to efficiently obtaining any required help.

Other than the content of the antipsychotic drug therapy, every healthcare professional, regardless of the specialty, must be able to communicate information. Information can be provided in spoken words, on paper, in drawings or icons, on a website, by e-learning, or in a short movie, depending on the preferences of the child or adolescent and the parents or caregivers. If a healthcare professional is well-acquainted with the antipsychotic drug treatment but cannot communicate at the level of the children, adolescents, parents, and caregivers, this may affect shared decision making due to a lack of knowledge, and it may be more difficult to achieve the desired results. Knowledge of the content of the therapy and the ability to communicate properly go hand in hand to provide tailored information, support the children and adolescents according to their needs, and involve the children, adolescents, parents, and caregivers.

4. Documentation and exchanging information

It is important that information regarding ADRs and monitoring outcomes are reported in the medical records of children and adolescents treated with

antipsychotic drugs. This makes the information easily available and also clear for other involved healthcare professionals, including the coordinating practitioner. The way in which this information is reported in medical records can differ between healthcare professionals. When we searched the electronic medical records of psychiatric outpatient clinics, as described in Chapter 3.2, we found that information can be reported at several places in the medical records, for example, in a table, uploaded as a file, or noted as free text. In addition, we found that the quality of notes differed between healthcare professionals, as some may record everything, some only the abnormalities, and others may use many abbreviations. This has also been shown in a study by Soto et al., who concluded that documentation in medical records varies, depending on the measure, and they found lower levels of documentation of medication.[28] Reporting at several places in the medical records and variations in documentation quality can lead to incomplete, unclear, or untraceable information, which can be a problem when retrieving information or if a colleague has to take over or needs information from the medical record.

Incomplete and unclear documentation in the medical records also influences the quality of information transferred externally, for example, from a psychiatric clinic to a general practitioner or pharmacist. The exchange of monitoring outcomes between healthcare professionals involved in antipsychotic drug treatment who work at different centers or clinics can be challenging as the systems are often not linked. Therefore, these outcomes are shared by email or mail, and subsequently added to the medical record as an uploaded file. These files may be difficult to find, and this will affect a simple overview of all monitoring outcomes, which is especially important for the coordinating practitioner. In addition, when only the monitoring outcomes are shared, the numbers are just data. Data becomes information when it is interpreted in the correct context. Therefore, additional information regarding the context, what the outcomes mean, and what the follow-up entails is necessary when exchanging monitoring outcomes and making it shared information. Not exchanging this valuable information may lead to mistakes and suboptimal antipsychotic drug treatment.

What is required to achieve this?

All monitoring outcomes and choices or considerations regarding whether or not to monitor a specific ADR-related parameter should be recorded in the electronic medical records. In Chapter 3.2 we showed that, currently, this is not being done. However, if the information is recorded clearly, it will be easier for the healthcare professional to retrieve information regarding monitoring for ADRs. In addition, it will be clearer and more transparent when information is transferred internally and externally to other healthcare professionals involved in the therapy of the child or adolescent, including the coordinating practitioner, to maintain an overview of the

therapy. To ensure that monitoring outcomes and considerations are recorded in the same place in the medical records and that documentation quality is similar, healthcare professionals working at the same clinic should agree on how the information and notes should be arranged. In addition, these agreements can be included in a work instruction and new employees can be trained accordingly. To support this effort, a healthcare system that is straightforward and easily applicable in daily clinical practice should be used.

In addition to recording all monitoring outcomes and choices in the medical records, other functionalities of these electronic medical records can be used or may be implemented to facilitate in organizing optimal monitoring. A study by Ramerman et al. has shown that healthcare professionals perceive electronic medical records as a burden, while it can be an extremely useful instrument.[26] For example, if the moments in time when monitoring should be performed are documented in the medical records in free text, it can easily be missed. An option to search for specific words in the medical records will make it easier to find previously reported information, especially in free text. In addition, a reminder system for when and for which parameters a child or adolescent should be monitored can be implemented, or a reminder can be generated for a later moment in time, when the outcomes are available and need to be assessed. If children and adolescents monitor their weight at home, they can access their own medical records from home and should be able to record the monitoring outcomes. The medical record can facilitate communication between the child or adolescent and the healthcare professional regarding the monitoring outcomes, occurred ADRs, or questions that arise. In addition, checklists for monitoring could pop-up when an antipsychotic drug is prescribed, listing the parameters that should be monitored and at what point during the antipsychotic drug treatment. Ideally, these lists should be adapted to the individual child or adolescent, including previous monitoring outcomes and comorbidities. Otherwise, these lists may be ignored or regarded as not applicable to this individual child or adolescent. Furthermore, when systems at different centers or clinics are linked, everyone involved will be able to obtain an overview of, for example, the healthcare professionals involved, the contact details of the coordinating practitioner, recent therapy, and the most recent monitoring outcomes. The child or adolescent and the parents or caregivers need to be involved with the exchange of information, as their consent is required. Therefore, also in this instance, the provision of information and shared decision making is important, and the purpose of sharing information with other healthcare providers must be emphasized. Although not all mentioned functionalities are currently included in the electronic medical records, these could help to optimize the monitoring process and improve drug safety.

5. Relevant adverse drug reaction-related parameters

Various ADR-related parameters can be monitored at the start of and during antipsychotic drug treatment, including physical (e.g., weight, body mass index, and blood pressure), laboratory (e.g., blood glucose, lipids, and prolactin), and observational (e.g., extrapyramidal symptoms) parameters, as is also shown in the three studies in Chapter 3. In addition to other previous studies, these three studies have shown that monitoring frequencies are irregular and generally low.[29,30] Although it is clear that antipsychotic drugs can cause weight gain and abnormal blood prolactin levels, there is no clear evidence available regarding the ADR-related parameters that should definitely be monitored to ensure drug safety. To define how children and adolescents should be monitored at the start of and during antipsychotic drug treatment, the parameters that are predictive of the occurrence of an ADR and the actions required if these parameters deviate from baseline or reference values need to be clear.

It does not only needs be clear which ADR-related parameters should be monitored, but also what the frequency of monitoring should be. There must be a balance in monitoring. A lack of monitoring or monitoring too frequently can affect the quality of life of a child or adolescent in different ways. When there is a lack of monitoring or the monitoring frequency is too low, ADRs can be missed, with serious consequences. For example, an increase in weight and abnormal blood glucose levels may lead to the development of diabetes mellitus, and hyperprolactinemia may cause sexual dysfunction or gynecomastia.[11,31] When ADR-related parameters are monitored too often, there will probably be a great overview of the effects of antipsychotic drug use, but this can also become a burden to the child or adolescent. For example, it can be stressful when a blood sample needs to be obtained from a child or adolescent, as it requires traveling time, drawing blood is not without risks, the child or adolescent may have a fear of needles, and, subsequently, they have to wait for the outcomes while they may be concerned about it. Monitoring weight may sound easier to achieve, but being weighed frequently can also be stressful, as the children and adolescents are constantly confronted by their drugs, reminded of their body weight and the ADRs that may occur, and possibly concerned about the outcome. A child or adolescent, as well as the parents or caregivers, may be concerned that therapy that is proving to be effective may have to be adjusted if there are severe and clinically relevant ADRs. Therefore, when the parameters that should be monitored are defined, a balance in the frequency of monitoring also must be found to achieve safe antipsychotic drug treatment.

What is required to achieve this?

To define what should be monitored to safely treat children and adolescents with antipsychotic drugs, it should be remembered what is "nice to know" and what is "needed to know." It is essential to know why a parameter must be monitored, whether a deviation in the parameter outcome can result in clinical risks for the child or adolescent, and what to do when the result is abnormal or deviates from earlier outcomes. Without this knowledge, the outcome of the parameter is mainly "nice to know" and not necessary to know, or the purpose of monitoring this parameter is unclear, and, therefore, the parameter should probably not be monitored. To define what ADR-related parameter outcomes are needed to know to ensure drug safety, the number needed to monitor (NNM) would add value. This number shows how many children or adolescents should be monitored for an ADR-related parameter to prevent the occurrence of one (severe) ADR. The NNMs will help to make it clearer what to expect regarding the occurrence of ADRs, and which ADR-related parameters have to be monitored to prevent harm.

More research is needed to calculate the NNMs. Before conducting a study, a clear definition of the NNM needs to be formulated. It needs to be defined whether only clinically relevant ADRs or also less severe ADRs will be considered to calculate the NNM. In addition, some ADRs, for example, somnolence, are more subjective and, therefore, more difficult to define, while blood levels are objective and easier to use in the calculation of an NNM. It should also be defined for every ADR which number is acceptable. When the NNM appears to be lower than this value, this ADR-related parameter does not need to be monitored or can be monitored less often. When the NNM appears to be greater, this ADR-related parameter should be monitored to ensure drug safety. After formulating a clear definition and deciding which parameters to include, a study needs to be conducted to gain more insight into monitoring and the occurrence of ADRs in children and adolescents treated with an antipsychotic drug to provide the required information to calculate the NNMs. For example, a prospective study that follows children and adolescents with a first prescription of an antipsychotic drug can be conducted. Monitoring the different ADR-related parameters in these children can reveal how many children develop ADRs that are clinically relevant. Although such a study would be valuable, it will be complex as several aspects need to be considered. There are differences in the ADRs that develop in different sex and age categories as well as in individual children and adolescents. For example, the use of other drugs, comorbidities, a family history of cardiac disorders, and other patient characteristics can influence the occurrence of ADRs. In addition, no child or adolescent will develop exactly the same ADRs and experience the ADRs in the same way. Nevertheless, a study to gain information to calculate the NNMs will support monitoring practices in daily life. The NNMs could help to make the monitoring more balanced. These numbers can

aid in determining what should be monitored and defining the optimal monitoring frequency, but possibly also the minimum monitoring frequency required to safely prescribe antipsychotic drugs to an individual child or adolescent and decrease the burden of monitoring.

6. Clear and easily applicable clinical practice guidelines

The monitoring required for ADRs in children and adolescents treated with antipsychotic drugs is described in the SmPCs of the specific antipsychotic drugs and in the CPGs.[32–38] The SmPC of the manufacturing pharmaceutical company includes information for healthcare professionals on the use of the drug, which can be adopted in CPGs. Despite the available CPGs, previous studies have shown that monitoring of children and adolescents treated with antipsychotic drugs is suboptimal.[39,40] This is also shown in Chapter 3, where we assessed monitoring practices in psychiatric outpatient clinics and by general practitioners. However, ultimately, regardless of the prescriber or the symptoms or disorder, a child or adolescent treated with an antipsychotic drug should be monitored for ADRs to ensure drug safety. It should be clearly described in a CPG how to achieve this and how to monitor each child or adolescent in a similar way that is also tailored to individual preferences and needs. In this way, CPGs can facilitate in the optimal monitoring for ADRs in children and adolescents.

Monitoring instructions, including the ADR-related parameters to monitor and the frequencies, differ in the CPGs, and they are not always clear and easily applicable in daily clinical practice,[41] as was also shown in Chapter 4.1. In addition, the monitoring instructions in CPGs are mostly general and rigid, and, therefore, not applicable to every child or adolescent. However, it is important to not adjust the child or adolescent to the available care and CPGs but to adjust the available care to the child or adolescent. Healthcare professionals need to be daring to deviate from the CPGs in a well-considered way. It can be challenging when a child or adolescent is prescribed an antipsychotic drug and it must be decided how to monitor a child with a fear of needles or an adolescent who does not always keep appointments, leading to a lack in monitoring. A clear description on how to monitor for ADRs in daily clinical practice is needed, but also advice on what the minimum monitoring frequency is for drug safety and on different options for monitoring when the "standard" is not applicable to an individual child or adolescent.

When the monitoring instructions are clear, they must be implemented in psychiatric clinics and general practices. There can be various barriers to guideline implementation that need to be considered, including a lack of evidence described in the CPG, a lack of applicability, or the physicians' lack of knowledge or agreement with the guideline.[42] After implementation, monitoring, evaluating, and adjusting

the CPG when necessary, according to the plan-do-check-act cycle, are important steps. The results in Chapter 4.1 as well as from other previous studies show that optimizing the current CPGs regarding implementation is recommended.[41,43] For example, our study showed that it was mainly poorly described how to apply the advice in the CPG locally. A clear CPG that is easily applicable in clinical practice can be a facilitator to conduct optimal antipsychotic drug monitoring in children and adolescents.

What is required to achieve this?

In this sixth topic, describing the need for a clear and easily applicable CPG, the previous described five topics that are required to achieve optimal monitoring in daily clinical practice come together. The first topic described above, shared decision making, is indispensable in successful antipsychotic drug treatment. It should be explained in the CPGs why it is important to involve the children, adolescents, parents, and caregivers in the antipsychotic drug treatment and to provide them with tailored information. In addition, to ensure that their needs and preferences are included in a CPG, it is advisable to involve the children, adolescents, parents, and caregivers in the developmental process of the CPG. Previous studies have shown that involving patients can emphasize the impact in daily life and lead to the incorporation of patient-relevant topics and outcomes.[44,45] They can also explain the barriers they experience regarding monitoring and concerns regarding the possible outcomes, and they could provide solutions for how to cope with these barriers and concerns. However, as shown in Chapter 4.1, the involvement of children, adolescents, parents, and caregivers was unclear and their preferences poorly incorporated in most CPGs. Their valuable contribution can make the CPGs less rigid and more applicable in daily life.

The CPGs should include sections regarding responsibility, education, and collaboration, as described above in the second and third topic. The role of a coordinating practitioner should be described. It should be clear that, although it is advisable to have a coordinating practitioner, there is a shared responsibility regarding antipsychotic drug treatment in children and adolescents, including all the involved healthcare professionals as well as the child or adolescent and parents or caregivers. They all have a responsibility to achieve drug safety. To be able to shoulder this responsibility, knowledge of antipsychotic drug treatment, education, access to reliable sources of information, communication, and collaboration are important aspects. Previous studies have shown that a lack of proper education and support and poor communication and collaboration with other healthcare professionals can be barriers for monitoring.[27,46] Healthcare professionals with different specialties should be involved in the developmental process of a CPG to advice on responsibility and required education and emphasize collaboration

between healthcare professionals, as they have insight into what is feasible in daily clinical practice.[47]

A section on the implementation of monitoring for ADRs in daily clinical practice is indispensable in a CPG. The CPGs should provide tools to implement the monitoring instructions, discuss evidence, and describe facilitators and barriers so that these can be considered.[14,47] As described in the fourth topic, electronic medical records can be an important facilitator in the implementation of monitoring. Advice on exploring the possibilities of the electronic medical records must be included in CPGs. For example, a reminder system that provides a reminder when monitoring should be performed, a checklist that lists what should be monitored when an antipsychotic drug is prescribed, or how to easily transfer information to healthcare professionals externally are aspects that can be considered. In addition, the importance of clearly reporting the monitoring outcomes and information related to monitoring should be emphasized, as, otherwise, this information cannot be retrieved, recent outcomes cannot be compared with previous outcomes, and monitoring could be meaningless. Specific advice on how to implement monitoring practices and report the information cannot be provided, as different healthcare systems are used and different agreements are preferred. However, there should be advice on how to implement the instructions included in the CPG locally and any considerations should be described.

Before clear monitoring instructions can be included in a CPG, more research is needed and NNMs should be calculated to be able to provide reliable and well-founded advice about monitoring, as described above in the fifth topic. These studies and the outcomes should be described in the CPGs to substantiate the advised monitoring instructions. The advice should include the general preferred monitoring practices and a minimum monitoring frequency to ensure drug safety. In addition, approaches to issues such as, for example, if there is a family history of cardiac disorders or a child has a fear of needles should be included. For the latter, an cream can be used to reduce the pain, and a previous study has shown that dry blood sampling may be described as an alternative to venipuncture in the future.[48] However, not all deviations can be captured in the CPGs; therefore, healthcare professionals still have to consider the individual preferences and needs of the child or adolescent and should be able to, well-considered, deviate from the CPGs.

Recommendations for future research, clinical practice, and education

More research is necessary to define how to optimally monitor children and adolescents treated with antipsychotic drugs. All the topics that are required to achieve optimal monitoring in daily clinical practice, as described above, should be studied in more detail. First, qualitative studies that include children, adolescents,

parents, caregivers, and different healthcare professionals involved in the antipsychotic drug treatment are recommended to establish what their needs, concerns, and preferences are. This can be done through interviews and with focus groups. Second, more research is needed on how to organize monitoring practices optimally, and to gain more insight into the role of the coordinating practitioner, collaboration between the various healthcare professionals, and the exchange of information internally and externally. In addition, more research is needed regarding the possibilities of electronic medical records, for example, reminder systems or checklists for ADR-related parameters when an antipsychotic drug is prescribed, to gain insight in what will support and improve monitoring practices and what should not be introduced into daily clinical practice. Third, quantitative studies that enable the calculation of the NNMs will be of great value by providing guidance on which ADR-related parameters should be monitored and with what frequency to ensure safe antipsychotic drug use in children and adolescents. More research in different areas will contribute to obtaining clear (national) CPGs that are applicable in daily clinical practice.

Healthcare professionals involved in antipsychotic drug treatment of children and adolescents should be aware of the effects of these drugs and the monitoring for ADRs. Therefore, education and refresher courses are essential and must be emphasized to keep pace with the latest developments, to provide tailored information to the child or adolescent and the parents or caregivers and to be able to discuss the treatment with other healthcare professionals. For the latter, interprofessional education (IPE), starting at the university, contributes to good communication and collaboration between healthcare professionals in daily practice, as students from different professions learn about, from, and with each other.[49] IPE should also be implemented in child and adolescent mental healthcare to improve the quality of care and health outcomes.[50] However, although every physician and pharmacist should know that monitoring for ADRs is important and why it is important, it is not realistic to expect that every healthcare professional should know everything about antipsychotic drug treatment in children and adolescents, as they are not all involved in such treatments. Regarding pharmacists, there are community pharmacists with an education and expertise in a specific area (*kaderapothekers),* and child and adolescent psychiatry should be included as possible specific area. The least every healthcare professional should know is where to find sources of reliable information, for example, on the internet or in CPGs, and which other healthcare professionals can advise them.

In addition, the children, adolescents, parents, and caregivers need to have adequate knowledge of antipsychotic drug treatment, including monitoring. There is a shared responsibility to ensure that antipsychotic drug treatment is successful. Healthcare professionals will provide information, but, for example, e-learning

about the (possible) effects of antipsychotic drugs and monitoring at home may add value, as not all information provided will be remembered and an e-learning course can be followed at any suitable time. These e-learnings should be easy, clear, and accessible so that the children, adolescents, and parents or caregivers are able to follow and understand it. In this way, they will not only learn more about the treatment but also be more involved and be able to discuss their own treatment with their healthcare professionals more easily.

Conclusion

Antipsychotic drugs can cause severe and bothersome ADRs in children and adolescents and, therefore, there is a need for monitoring. However, the findings from this thesis show that monitoring practices by healthcare professionals differ and are suboptimal. The monitoring required for ADRs in children and adolescents treated with antipsychotic drugs is described in the CPGs. However, monitoring instructions, including which ADRs to monitor and the frequencies, differ in the CPGs, and they are not always clear and easily applicable in daily clinical practice. There is a lack of evidence on how monitoring should be performed, and, therefore, it is difficult to include clear and well-founded monitoring instructions in CPGs. More knowledge about what should be monitored and the frequency of monitoring is needed, as well as more insight in how to organize these monitoring practices. The organization can be challenging as various healthcare professionals are involved during antipsychotic drug treatment, for example, child and adolescent psychiatrists and general practitioners. They need to share information and knowledge to provide the most optimal care. It is also important to involve the child or adolescent and the parents or caregivers, as shared decision making is indispensable in attaining success with the antipsychotic drug treatment, including monitoring. The children, adolescents, parents, caregivers, and healthcare professionals involved have a shared responsibility during the antipsychotic drug treatment. The terms shared information, shared knowledge, shared decision making, and shared responsibility emphasize that optimal monitoring for ADRs in children and adolescents treated with antipsychotic drugs can only be achieved through collaboration. This way, ADRs can be detected at an early stage to adjust the therapy as required, according to the individual needs and preferences of the child or adolescent, and to achieve a safe antipsychotic drug treatment for this young and vulnerable population.

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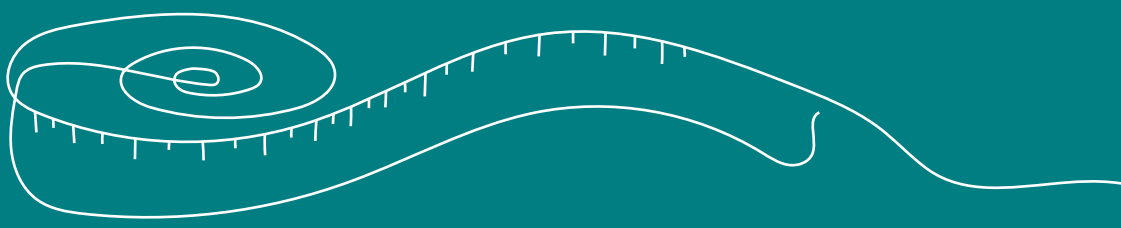


Chapter 6

Summary & Samenvatting

Chapter 6.1

Summary

Psychiatric symptoms and disorders, such as behavioral disorders, irritability associated with autism, eating disorders, tic disorders, and attention-deficit/hyperactivity disorder, can affect children and adolescents in daily life. Treatment may include pharmacotherapy with antipsychotic drugs. In order to determine the optimal treatment, and to decide whether pharmacotherapy is indicated, the World Health Organization's (WHO) Guide to Good Prescribing recommends a six-step process: 1) defining the problem, 2) specifying the therapeutic objective, 3) reviewing available treatment options and evidence from sources like clinical practice guidelines (CPGs), 4) selecting the best treatment for the individual child or adolescent, 5) providing clear information and instructions, and 6) monitoring and evaluating the treatment and making adjustments when necessary. When prescribing antipsychotic drugs to a child or adolescent, it is important to be aware of the potential for severe adverse drug reactions (ADRs) such as weight gain, gynecomastia, abnormal blood glucose levels, and extrapyramidal effects. This emphasizes the importance of monitoring the therapy (step six) to identify ADRs in a timely manner. The potential for ADRs and the need for monitoring may also impact treatment selection (step four), and should be included in the information and instructions provided to the children, adolescents, parents, and caregivers (step five). It is crucial to provide clear information and support, as ADRs and monitoring may have physical, emotional, and social impact on the child or adolescent's life. In addition, having a deeper understanding of their own therapy may enhance shared decision making. However, it is not clear how to optimally monitor children and adolescents treated with antipsychotic drugs, as CPGs differ in advice and there is limited evidence available on which ADR-related parameters should be monitored for drug safety. This makes it challenging to provide clear monitoring instructions and guidance for daily practice.

The aim of this thesis was to assess the daily clinical practice of monitoring for ADRs of antipsychotic drugs in children and adolescents, including the facilitators for and barriers to monitoring.

Need for monitoring

The need for monitoring for ADRs in children and adolescents treated with antipsychotic drugs was addressed in **Chapter 2**. In **Chapter 2.1** the frequencies of spontaneously reported ADRs in children and adolescents treated with antipsychotic drugs were determined using data from the worldwide database VigiBase. The study included individual case safety reports from 1968 until March 2017 in which an antipsychotic drug was the suspected or interacting drug. Proportional reporting ratios (PRRs) and 95% confidence intervals (95% CIs) were calculated for genders, age classes, and reporter types. A wide range of ADRs were reported in children and adolescents treated with antipsychotic drugs. In total, 45,201 reported ADRs were included. The most commonly reported ADRs were those related to extrapyramidal

syndrome (14.7%), breast disorders or blood prolactin level changes (4.7%), and cardiac arrhythmias (4.6%). Differences in relative reporting frequencies were observed between age classes and reporter types, and to a lesser extent between genders. For example, ADRs related to hyperglycemia/new-onset diabetes mellitus were less frequently reported in children aged 1 - 5 than in children aged 12 - 17 years (PRR: 0.4, 95% CI: 0.2 - 0.5). ADRs related to cardiac arrhythmias were less frequently reported by consumers compared to health care professionals (PRR: 0.5, 95% CI: 0.5 - 0.6), while ADRs related to changes in weight/body mass index were more frequently reported by consumers (PRR: 3.2, 95% CI: 2.9 - 3.5). It is possible that consumers mainly report ADRs that affect the child's quality of life and are burdensome, while health care professionals may not always regard these ADRs as posing a significant health risk and may report on more objectively examined ADRs. The relative differences in reporting frequency between age classes and reporter types can be useful for tailoring information about possible ADRs and for monitoring for ADRs.

Monitoring in daily clinical practice

Although it is known that antipsychotic drugs can cause severe ADRs, there is a lack of information on how children and adolescents treated with these drugs are monitored. In **Chapter 3**, the daily clinical practice of monitoring by healthcare professionals was examined. **Chapter 3.1** focused on how healthcare professionals in the Netherlands report on monitoring for ADRs in children and adolescents treated with antipsychotic drugs. To gather this information, a questionnaire was designed and distributed at a national conference. It was completed by 59 healthcare professionals, of whom 53 (89.8%) were child and adolescent psychiatrists. More respondents reported monitoring physical parameters (>80%), including weight, height, body mass index, heart rate, and blood pressure, than laboratory parameters (>50%), including lipid profile, blood glucose, and prolactin level. Most of the respondents reported monitoring physical parameters more than twice per year and laboratory parameters once per year. Respondents cited insufficient availability of resources like electrocardiogram facilities as barriers to monitoring. Almost all respondents (94.9%) reported using a clinical guideline or protocol for monitoring, but only one respondent reported monitoring completely according to the clinical guideline. These findings indicate significant variability in reported monitoring practices among healthcare professionals.

Chapter 3.2 assessed the actual monitoring of children and adolescents taking antipsychotic drugs in daily clinical practice by reviewing the medical records of psychiatric outpatient clinics. This retrospective follow-up study included 100 randomly selected outpatients aged 18 years or younger who had a first prescription for an antipsychotic drug recorded in the electronic medical records of psychiatric outpatient clinics between 2014 and 2017. They were followed for

up to three years. This study evaluated the frequency of monitoring for physical parameters (weight, height, body mass index, waist circumference, pulse, blood pressure, and an electrocardiogram) and laboratory parameters (glucose, lipids, and prolactin) parameters. Monitoring frequencies were stratified by the patient characteristics (sex, age, cardiovascular risk factors, and use of other psychotropic drugs), and by location of antipsychotic drug initiation (psychiatric outpatient clinic or elsewhere). The monitoring frequencies varied. Overall, physical parameters were monitored more frequently (weight: 85.9% during the first half-year) than laboratory parameters (glucose and cholesterol: both 23.5%). In total, 3% of the children and adolescents were never monitored for any physical parameter, and 54% were never monitored for any laboratory parameter. Reasons for not monitoring were rarely recorded in the medical records. For a minority of the children (14.8%) who were never monitored for laboratory parameters, reasons such as refusal by the child or parents and monitoring performed by the general practitioner or elsewhere were recorded.

Chapter 3.3 also showed low monitoring frequencies among general practitioners. For this retrospective follow-up study, data recorded in the Clinical Practice Research Datalink (CPRD) between 2000 and 2017 were used. This study included children, youth, and young adults aged 0 - 24 years, who had an initial prescription of a second generation antipsychotic drug (SGA) recorded and were prescribed an SGA more than once for a duration of at least six months. It was assessed which ADR-related physical parameters (weight, height, body-mass index, waist circumference, pulse, blood pressure, and heart examination) and laboratory parameters (glucose, HbA1c, lipids, and prolactin) in children, youth, and young adults were monitored at least once every 6-month period. Data were stratified by sex, age categories, and calendar years. In total, 7,006 patients were included and the mean duration of follow-up was 1.6 years. Monitoring frequencies of all parameters were below 25%. Blood pressure and weight were monitored in 23.6% and 23.4%, respectively, of all children, youth, and young adults during the first half year; waist circumference was monitored in 0.2%. Females were monitored more often than males, some differences between age categories were observed, and monitoring frequencies increased after the year 2000, but did not exceed 35% in any year. This study as well as the studies in Chapter 3.1 and 3.2 showed that monitoring frequencies varied, and especially the monitoring frequencies of laboratory parameters were low.

Support during antipsychotic drug treatment

Antipsychotic drugs can cause severe ADRs and monitoring is crucial to ensure the safety of the children and adolescents during treatment. Therefore, the healthcare professionals as well as the children, adolescents, parents, and caregivers should be provided with clear instructions and information. In **Chapter 4** the support provided regarding antipsychotic drug use was addressed. In **Chapter 4.1** the clarity of

presentation and the applicability of ADR-related monitoring instructions in CPGs for children and adolescents treated with antipsychotic drugs were assessed. Guidelines from six different countries were selected, and monitoring instructions for 13 ADR-related parameters were assessed. The Appraisal of Guidelines for Research and Evaluation (AGREE) instrument and the Systematic Information for Monitoring (SIM) score were used to assess the clarity and applicability of the monitoring instructions in each CPG. Although the presentation of the monitoring instructions was clear in all of them, the applicability was found lacking, with all CPGs scoring lower in this regard. For example, barriers and facilitators to monitoring were poorly described. The number of ADR-related parameters included in the CPGs varied between 8 and 13. The importance of monitoring each parameter was always described, and while the timing to start monitoring was also often described (90.2%), the timing to stop monitoring was less frequently addressed (37.4%). This study showed that the CPGs differed on the parameters that needed to be monitored. Especially the applicability needs to be improved to provide better guidance on monitoring ADRs in daily clinical practice.

Chapter 4.2 focused on the support provided to adolescents during antipsychotic drug treatment and their experiences, needs, preferences, and suggestions for improvement. Two adolescents with a tic disorder who had been treated with antipsychotic drugs for at least three months were interviewed online. Their experiences differed. While one was satisfied with the support received, the other did not receive sufficient support to know what to expect and how to cope with ADRs. Their need for support was rather similar, as they both expressed a need for personal contact with healthcare professionals and to be involved in decision making. These preliminary results suggest that support should be personalized to meet the individual needs of adolescents taking antipsychotic drugs.

Conclusion

Antipsychotic drugs can cause severe and bothersome ADRs in children and adolescents, making monitoring essential. However, this thesis showed that monitoring practices of healthcare professionals are suboptimal and vary. CPGs provide guidance on monitoring for ADRs in children and adolescents treated with antipsychotic drugs, but the instructions differ across CPGs and are not always clear or easily applicable in daily practice. There is a lack of evidence on the optimal way to monitor, making it difficult to include clear, well-founded monitoring instructions in CPGs. To improve monitoring practices, more knowledge is needed on what and how frequently to monitor, as well as on how to organize these practices effectively with the involvement of various healthcare professionals, such as child and adolescent psychiatrists, general practitioners, and pharmacists. They need to share information and knowledge to provide the most optimal care. It is also important to involve the child or adolescent and the parents or caregivers, as

shared decision making is crucial for a successful antipsychotic drug treatment, including monitoring. The children, adolescents, parents, caregivers, and healthcare professionals involved have a shared responsibility during the antipsychotic drug treatment. The terms shared information, shared knowledge, shared decision making, and shared responsibility emphasize that optimal monitoring for ADRs in children and adolescents treated with antipsychotic drugs can only be achieved through collaboration. By working together and sharing information and responsibilities, ADRs can be detected early and the antipsychotic drug treatment can be adjusted according to the individual needs and preferences of the child or adolescent, ensuring a safe and effective antipsychotic drug treatment for this vulnerable population.

Recommendations for future research, clinical practice, and education

Further research is needed to optimize monitoring for ADRs in children and adolescents treated with antipsychotic drugs. Qualitative studies that involve a range of stakeholders, including children, adolescents, parents, caregivers, and healthcare professionals, can provide insight into the needs, concerns, and preferences of those involved in antipsychotic treatment. In addition, research on how to organize monitoring practices and the collaboration between healthcare professionals as well as the exchange of (digital) information internally and externally is necessary. Quantitative studies can provide guidance on which ADR-related parameters should be monitored and the frequency of monitoring to ensure safe antipsychotic drug use in children and adolescents. This research can contribute to the development of clear and applicable CPGs for daily clinical practice.

It is important that healthcare professionals involved in the antipsychotic drug treatment of children and adolescents are aware of the effects of these drugs and the importance of monitoring for ADRs. Continuing education and refresher courses can help ensure that healthcare professionals have up-to-date knowledge and can provide tailored information to children, adolescents, parents, and caregivers. It is also meaningful that children, adolescents, parents, and caregivers have a good understanding of the antipsychotic drug treatment and monitoring. Healthcare professionals can provide this information, but e-learning resources or short videoclips may also be helpful. There is a shared responsibility to ensure that the antipsychotic drug treatment is successful.

Chapter 6.2

Samenvatting

Kinderen en adolescenten kunnen antipsychotica voorgeschreven krijgen ter behandeling van verschillende psychiatrische symptomen en stoornissen, zoals gedragsstoornissen, agressief gedrag dat samen kan hangen met autisme, eetstoornissen, ticstoornissen en aandachtsdeficiëntie/hyperactiviteitsstoornis (ADHD). Voor de selectie van de meest geschikte behandeling en om te bepalen of farmacotherapie met een antipsychoticum geïndiceerd is, beveelt de Wereldgezondheidsorganisatie (WHO) Guide to Good Prescribing een behandelplan aan dat bestaat uit zes stappen: 1) definiëren van het probleem, 2) vaststellen van het therapeutische doel van de behandeling, 3) beoordelen van behandelingsmogelijkheden, waarbij gebruik wordt gemaakt van bronnen zoals klinische richtlijnen, 4) selecteren van de meest geschikte behandeling voor het individuele kind of de adolescent, 5) verstrekken van duidelijke informatie en instructies en 6) monitoren en evalueren van de behandeling en deze aanpassen indien nodig. Wanneer behandeling met een antipsychoticum gewenst is, moet de voorschrijver zich bewust zijn van de mogelijke ernstige bijwerkingen die hierbij kunnen optreden, zoals gewichtstoename, gynaecomastie (borstvorming) en extrapiramidale effecten (motorische problemen). Het monitoren van het eventueel optreden van bijwerkingen is van belang om deze tijdig te kunnen identificeren (stap 6 uit de WHO-richtlijn). Dit kan onder andere gedaan worden aan de hand van lichamelijke parameters, zoals gewicht en bloeddruk, laboratoriumparameters, zoals bloedglucose, lipidenprofiel en prolactinespiegels, en observationele parameters, zoals veranderingen in bewegingen. Het risico op ernstige bijwerkingen en de noodzaak om te monitoren kunnen van invloed zijn op de keuze van de behandeling voor het kind of de adolescent (stap vier). Tevens moeten informatie en instructies hieromtrent worden verstrekt aan de kinderen, adolescenten, ouders en verzorgers (stap vijf). Het is van belang om ondersteuning te bieden aan kinderen en adolescenten die behandeld worden met een antipsychoticum, omdat de mogelijke bijwerkingen en het monitoren hierop zowel lichamelijke consequenties kunnen hebben als een emotionele en sociale impact op het dagelijks leven. Daarnaast kan een beter begrip van de eigen therapie de gedeelde besluitvorming (shared decision making) bevorderen. Het is echter niet duidelijk hoe kinderen en adolescenten die behandeld worden met een antipsychoticum optimaal te monitoren op bijwerkingen. Klinische richtlijnen verschillen in hun advies en er is slechts beperkt bewijs beschikbaar op basis van onderzoek over welke bijwerkingen gemonitord moeten worden en hoe dit precies moet gebeuren. Dit maakt het lastig om duidelijke instructies en richtlijnen op te stellen voor de dagelijkse praktijk.

Het doel van dit proefschrift was het beoordelen van het monitoren van bijwerkingen in de dagelijkse praktijk bij kinderen en adolescenten die behandeld worden met antipsychotica, inclusief de bevorderende en belemmerende factoren voor het monitoren.

Noodzaak van monitoren

In **Hoofdstuk 2** wordt ingegaan op de noodzaak van het monitoren van bijwerkingen bij kinderen en adolescenten die behandeld worden met antipsychotica. In **Hoofdstuk 2.1** zijn spontaan gemelde bijwerkingen op een rij gezet en geanalyseerd. Hiervoor zijn gegevens uit de wereldwijde database VigiBase gebruikt en zijn individuele meldingen geïncludeerd van 1968 tot maart 2017 waarbij een antipsychoticum het vermoedelijke of interacterende geneesmiddel was. Proportional reporting ratios (PRR's) en 95%-betrouwbaarheidsintervallen (95% BI) zijn berekend voor geslacht, leeftijdscategorieën en type melders. Bij kinderen en adolescenten die behandeld werden met antipsychotica is een breed scala aan bijwerkingen gemeld. Voor dit onderzoek werden in totaal 45.201 gemelde bijwerkingen geïncludeerd. De meest gemelde bijwerkingen waren die gerelateerd aan het extrapiramidaal syndroom (14,7%), borstaandoeningen of veranderingen in het prolactinegehalte in het bloed (4,7%) en hartritmestoornissen (4,6%). Verschillen in gemelde bijwerkingen werden voornamelijk waargenomen tussen leeftijdscategorieën en tussen type melders, en in mindere mate tussen jongens en meisjes. Bijwerkingen gerelateerd aan hyperglykemie/het ontstaan van diabetes mellitus werden bijvoorbeeld minder vaak gemeld bij kinderen van 1 – 5 jaar dan bij kinderen van 12 – 17 jaar oud (PRR: 0,4, 95% BI: 0,2 – 0,5). Bijwerkingen gerelateerd aan hartritmestoornissen werden minder vaak gemeld door consumenten dan door zorgprofessionals (PRR: 0,5, 95% BI: 0,5 – 0,6), terwijl bijwerkingen gerelateerd aan veranderingen in gewicht/body mass index vaker werden gemeld door consumenten (PRR: 3,2, 95% BI: 2,9 – 3,5). Het is mogelijk dat consumenten, waaronder kinderen en ouders, vooral bijwerkingen melden die impact hebben op de kwaliteit van leven van het kind, terwijl zorgprofessionals deze bijwerkingen niet altijd als een significant gezondheidsrisico beschouwen en meer objectief gemeten bijwerkingen melden. Inzicht in de verschillen in meldingen tussen de leeftijdscategorieën en tussen type melders kan helpen bij het op maat verstrekken van informatie aan kinderen en adolescenten over de mogelijke bijwerkingen en het monitoren hierop.

Monitoring in de dagelijkse klinische praktijk

Ondanks dat het bekend is dat antipsychotica ernstige bijwerkingen kunnen veroorzaken, is het onduidelijk hoe kinderen en adolescenten die met deze geneesmiddelen worden behandeld, worden gemonitord. In **Hoofdstuk 3** is gekeken naar het monitoren door zorgprofessionals in de dagelijkse klinische praktijk. Voor het onderzoek in **Hoofdstuk 3.1** is aan voorschrijvers gevraagd hoe zij kinderen en adolescenten die een antipsychoticum gebruikten monitorden op bijwerkingen. Hiervoor is een vragenlijst opgesteld welke is uitgedeeld op een nationaal congres voor kinder- en jeugdpsychiatrie. In totaal vulden 59 voorschrijvers de vragenlijst in, onder wie 53 (89,8%) kinder- en jeugdpsychiaters. Meer respondenten rapporteerden het monitoren van lichamelijke parameters (>80%), waaronder gewicht, lengte, body mass index, hartslag en bloeddruk, dan laboratoriumparameters (>50%), waaronder

lipidenprofiel, bloedglucose en prolactinespiegel. De meeste respondenten meldden dat zij de lichamelijke parameters meer dan twee keer per jaar monitorden en laboratoriumparameters één keer per jaar. Een belemmering voor het monitoren was onder andere onvoldoende beschikbare middelen, zoals faciliteiten voor het maken van een elektrocardiogram. Bijna alle respondenten (94,9%) meldden dat ze een klinische richtlijn of protocol volgden voor het monitoren van de kinderen en adolescenten, maar slechts één van alle respondenten monitorde volledig volgens de klinische richtlijn, uitgaande van de antwoorden gegeven in de vragenlijst. Deze bevindingen duiden op een verschil in wijze van monitoren tussen voorschrijvers, waarbij er zowel een verschil in frequentie is als in welke parameters er gemonitord worden.

Om een beter beeld te krijgen hoe daadwerkelijk gemonitord wordt op bijwerkingen in de dagelijkse praktijk, is dit in **Hoofdstuk 3.2** nader onderzocht door middel van inzage in medische dossiers van kinderen en adolescenten die poliklinisch behandeld werden met een antipsychoticum. Dit retrospectieve onderzoek omvatte 100 willekeurig geselecteerde poliklinische patiënten van 18 jaar of jonger die tussen 2014 en 2017 een eerste recept voor een antipsychoticum voorgeschreven hadden gekregen bij een psychiatrische instelling. Ze werden gevolgd voor een periode van maximaal drie jaar. Bij deze jongeren is gekeken naar de frequentie van monitoren van lichamelijke parameters (gewicht, lengte, body mass index, tailleomtrek, pols, bloeddruk en een elektrocardiogram) en laboratoriumparameters (glucose, lipiden en prolactine). Er is gestratificeerd op basis van de kenmerken van de patiënt (geslacht, leeftijd, cardiovasculaire risicofactoren en gebruik van andere psychofarmaca) en op locatie van het eerste voorschrift van het antipsychoticum (psychiatrische polikliniek of elders). De frequentie van monitoren van bijwerkingen varieerde. Over het algemeen werden lichamelijke parameters vaker gemonitord (gewicht: bij 85,9% van de kinderen en adolescenten in het eerste half jaar) dan laboratoriumparameters (glucose en cholesterol: beide bij 23,5%). In totaal werd 3% van de kinderen en adolescenten nooit gemonitord op lichamelijke parameters en 54% nooit op laboratoriumparameters. Redenen om niet te monitoren werden zelden vastgelegd in de medische dossiers. Bij enkele kinderen (14,8%) die nooit werd gemonitord op laboratoriumwaarden, zijn redenen geregistreerd als weigering door het kind of de ouders en monitoring door de huisarts of elders.

In **Hoofdstuk 3.3** is gekeken naar het monitoren van bijwerkingen door huisartsen. Voor dit retrospectieve onderzoek zijn gegevens gebruikt uit de Clinical Practice Research Datalink (CPRD) uit het Verenigd Koninkrijk tussen 2000 en 2017. Er zijn kinderen, adolescenten en jongvolwassenen geïncludeerd van 0 – 24 jaar oud, voor wie een eerste recept voor een atypisch antipsychoticum in deze database stond en die meer dan eens een atypisch antipsychoticum kregen voorgeschreven voor in totaal een periode van ten minste zes maanden. Er is gekeken welke lichamelijke

parameters (gewicht, lengte, body-mass index, middelomtrek, pols, bloeddruk en hartonderzoek) en laboratoriumparameters (glucose, HbA1c, lipiden en prolactine) bij kinderen, adolescenten en jongvolwassenen ten minste eenmaal per 6 maanden gemonitord werden. Er is gestratificeerd naar geslacht, leeftijdscategorieën en kalenderjaren. In totaal werden 7.006 patiënten geïncludeerd en de gemiddelde duur van de follow-up was 1,6 jaar. Ook dit onderzoek liet zien dat de frequentie van monitoren laag was. De bloeddruk en het gewicht werden bij respectievelijk 23,6% en 23,4% van alle kinderen, jongeren en jongvolwassenen gedurende het eerste half jaar gemonitord; de tailleomtrek werd gemonitord bij 0,2%. Alle percentages waren lager dan 25%. Verder werden vrouwen vaker gemonitord dan mannen, werden enkele verschillen tussen leeftijdscategorieën waargenomen en namen de frequenties van monitoren toe na het jaar 2000, maar kwam dit in geen enkel jaar boven de 35% uit. Zowel dit onderzoek als de onderzoeken in hoofdstuk 3.1 en 3.2 laten zien dat de frequentie van monitoren varieert en vooral de frequentie van het monitoren van laboratoriumparameters laag is.

Ondersteuning tijdens de behandeling met antipsychotica

Gebruik van antipsychotica kan ernstige bijwerkingen met zich meebrengen. Het monitoren van deze bijwerkingen is van belang om de veiligheid van kinderen en adolescenten tijdens de behandeling te waarborgen. Daarom moeten zowel zorgprofessionals als de kinderen, adolescenten, ouders en verzorgers duidelijke instructies en informatie hierover krijgen. In **Hoofdstuk 4** is gekeken naar de ondersteuning die geboden wordt bij het voorschrijven en het gebruik van antipsychotica. In **Hoofdstuk 4.1** zijn monitorinstructies zoals die zijn beschreven in klinische richtlijnen beoordeeld op duidelijkheid van presentatie en toepasbaarheid in de klinische praktijk. Hiervoor zijn klinische richtlijnen uit zes verschillende landen geselecteerd, waarna de monitorinstructies voor 13 bijwerking-gerelateerde parameters zijn beoordeeld. De duidelijkheid en toepasbaarheid van de instructies zijn met behulp van de Appraisal of Guidelines for Research and Evaluation (AGREE) tool en de Systematic Information for Monitoring (SIM) score beoordeeld. De presentatie van de monitorinstructies was voor alle parameters duidelijk. Echter, de toepasbaarheid ontbrak veelal en alle richtlijnen scoorden lager op dit punt. Belemmerende en faciliterende factoren voor het monitoren werden bijvoorbeeld onvoldoende beschreven. Het aantal bijwerking-gerelateerde parameters opgenomen in de klinische richtlijnen varieerde tussen 8 en 13. Het belang van het monitoren werd in iedere richtlijn beschreven voor al deze parameters. Tevens werd vaak aangegeven wanneer te starten met het monitoren (90,2%), terwijl het niet altijd duidelijk was wanneer te stoppen (37,4%). Dit onderzoek toonde aan dat de richtlijnen verschilden in welke parameters er gemonitord moesten worden en vooral de toepasbaarheid van de richtlijnen en instructies verdient aandacht. Dit aspect moet opgenomen en verbeterd worden in klinische richtlijnen om betere

instructies te bieden aan zorgprofessionals omtrent het monitoren van bijwerkingen in de dagelijkse klinische praktijk.

In **Hoofdstuk 4.2** is gekeken naar de begeleiding die geboden wordt door zorgprofessionals aan adolescenten tijdens de behandeling met antipsychotica. Daarbij is onderzocht wat de ervaringen, behoeften, voorkeuren en suggesties voor verbetering zijn van de adolescenten. Online werden twee adolescenten met een ticstoornis geïnterviewd die minimaal drie maanden een antipsychoticum gebruikten. Hun ervaringen rondom de begeleiding liepen uiteen. Terwijl de één tevreden was met de ontvangen begeleiding, ervaarde de ander onvoldoende ondersteuning om te weten wat zij kon verwachten en hoe zij met de bijwerkingen moest omgaan. Wel was hun behoefte aan begeleiding vergelijkbaar, aangezien ze allebei behoefte hadden aan persoonlijk contact met zorgprofessionals en wilden zij betrokken worden bij de besluitvorming. Deze voorlopige resultaten suggereren dat persoonlijke begeleiding belangrijk is om tegemoet te komen aan de individuele behoeften van adolescenten die antipsychotica gebruiken.

Conclusie

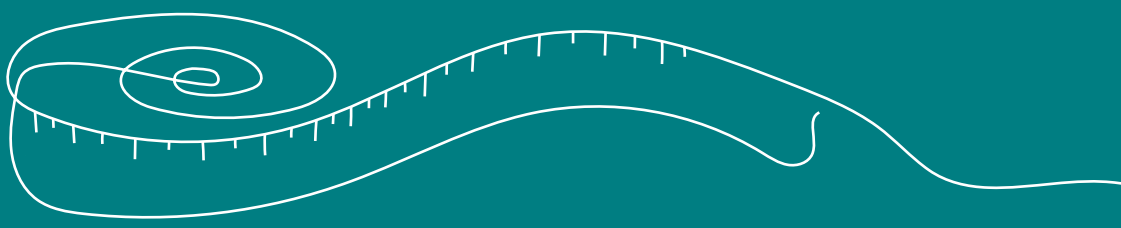
Antipsychotica kunnen bij kinderen en adolescenten ernstige en hinderlijke bijwerkingen veroorzaken, waardoor monitoren van belang is. Dit proefschrift toonde echter aan dat de wijze van monitoren in de dagelijkse praktijk suboptimaal is en sterk varieert. Klinische richtlijnen bieden instructies voor het monitoren van bijwerkingen bij kinderen en adolescenten die worden behandeld met antipsychotica, maar de instructies verschillen per richtlijn en zijn niet altijd duidelijk of gemakkelijk toepasbaar in de dagelijkse praktijk. Er is een gebrek aan bewijs over wat de optimale manier van monitoren is, wat het lastig maakt om duidelijke, goed onderbouwde instructies op te nemen in richtlijnen. Om het monitoren in de dagelijkse praktijk te verbeteren, is meer kennis nodig over wat en hoe vaak gemonitord moet worden voor een veilig gebruik van antipsychotica door kinderen en adolescenten. Daarnaast is meer inzicht nodig in hoe dit georganiseerd kan worden met betrokkenheid van verschillende zorgprofessionals, zoals kinder- en jeugdpsychiaters, huisartsen en apothekers. Zij moeten informatie en kennis delen om de meest optimale zorg te kunnen bieden. Hierbij is het ook van belang het kind of de adolescent en de ouders of verzorgers te betrekken, aangezien gezamenlijke besluitvorming cruciaal is voor een succesvolle behandeling met antipsychotica, inclusief het monitoren. De betrokken kinderen, jongeren, ouders, verzorgers en zorgprofessionals hebben een gedeelde verantwoordelijkheid tijdens de behandeling met antipsychotica. De termen gedeelde informatie, gedeelde kennis, gedeelde besluitvorming en gedeelde verantwoordelijkheid benadrukken dat het optimaal monitoren van bijwerkingen bij kinderen en adolescenten die worden behandeld met antipsychotica alleen kan worden bereikt door middel van samenwerking. Door samen te werken en informatie en verantwoordelijkheden te

delen, kunnen bijwerkingen vroegtijdig worden opgespoord en kan de behandeling met antipsychotica worden aangepast aan de individuele behoeften en voorkeuren van het kind of de adolescent. Hierdoor kan een veilige en effectieve behandeling met antipsychotica voor deze kwetsbare groep worden bewerkstelligd.

Aanbevelingen voor toekomstig onderzoek, de klinische praktijk en onderwijs

Verder onderzoek is nodig om het monitoren van bijwerkingen bij kinderen en adolescenten die met antipsychotica worden behandeld te optimaliseren. Kwalitatief onderzoek waarbij verschillende belanghebbenden betrokken worden, waaronder kinderen, adolescenten, ouders, verzorgers en zorgprofessionals, kan inzicht verschaffen in hun behoeften, zorgen en voorkeuren rondom de behandeling. Daarnaast is onderzoek nodig naar de organisatie van het monitoren, de samenwerking tussen zorgprofessionals en de uitwisseling van (digitale) informatie intern en extern. Kwantitatief onderzoek kan meer inzicht geven in welke parameters gemonitord moeten worden en hoe vaak om veilig gebruik van antipsychotica door kinderen en adolescenten te waarborgen. Deze onderzoeken kunnen bijdragen aan de ontwikkeling van duidelijke en toepasbare richtlijnen voor de dagelijkse klinische praktijk.

Zorgprofessionals die betrokken zijn bij de behandeling van kinderen en adolescenten met antipsychotica moeten op de hoogte zijn van de effecten van deze geneesmiddelen en van het belang van het monitoren van bijwerkingen. Onderwijs en nascholing kunnen ervoor zorgen dat zorgprofessionals up-to-date kennis hebben en begeleiding op maat kunnen bieden aan kinderen, adolescenten, ouders en verzorgers. Daarnaast is het ook van belang dat de kinderen, adolescenten, ouders en verzorgers een goed begrip hebben van de behandeling met antipsychotica en het monitoren van bijwerkingen. Zorgprofessionals kunnen deze informatie geven, maar ook een e-learning op maat of korte filmpjes over dit onderwerp kunnen nuttig zijn. Er is een gedeelde verantwoordelijkheid om ervoor te zorgen dat de behandeling met antipsychotica slaagt.



Chapter 7

Appendices

7.1 DANKWOORD

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7.4 AUTHOR'S CONTRIBUTION

Chapter 1 Introduction

LM wrote the general introduction of this thesis. Her PhD supervisors commented on previous versions of the manuscript and LM implemented their feedback.

Chapter 2 Need for monitoring

2.1 Reported adverse drug reactions in children and adolescents treated with antipsychotics

LM designed the study, collected and analyzed the data, interpretated the results, and wrote the manuscript. All authors contributed to and commented on these aspects. LM implemented their feedback.

Chapter 3 Monitoring in daily clinical practice

3.1 Monitoring of metabolic, cardiac, and endocrine indicators in youth treated with antipsychotics as reported by health care professionals

LM designed the study, collected and analyzed the data, interpretated the results, and wrote the manuscript. All authors contributed to and commented on these aspects. LM implemented their feedback.

3.2 Monitoring of adverse drug reaction-related parameters in children and adolescents treated with antipsychotic drugs in psychiatric outpatient clinics

LM designed the study, collected and analyzed the data, interpretated the results, and wrote the manuscript. All authors contributed to and commented on these aspects. LM implemented their feedback.

3.3 Monitoring of adverse drug reaction-related parameters in children, youth, and young adults prescribed antipsychotic drugs by general practitioners

LM designed the study, collected and analyzed the data, interpretated the results, and wrote the manuscript. All authors contributed to and commented on these aspects. LM implemented their feedback.

Chapter 4 Support during antipsychotic drug treatment

4.1 Clarity and applicability of adverse drug reaction-related monitoring instructions in clinical practice guidelines for children and adolescents treated with antipsychotic drugs: a review of six clinical practice guidelines

LM designed the study, collected and analyzed the data, interpretated the results, and wrote the manuscript. All authors contributed to and commented on these aspects. LM implemented their feedback.

4.2 Support from healthcare professionals during antipsychotic drug treatment: experiences of adolescents with a tic disorder

LM designed the study, collected and analyzed the data, interpretated the results, and wrote the manuscript. All authors contributed to and commented on these aspects. LM implemented their feedback.

Chapter 5 General discussion

LM wrote the general discussion of this thesis. Her PhD supervisors commented on previous versions of the manuscript and gave advice.

7.5 ABOUT THE AUTHOR

Lenneke Minjon was born in 1986 in Nieuwegein, the Netherlands. She obtained her Bachelor's degree in 2007, and in 2011 her Master's degree in Pharmacy at Utrecht University. She performed her research internship on Parkinson's Disease at the UCL School of Pharmacy in London.

After her graduation, she worked as a pharmacist at various outpatient and community pharmacies; the outpatient pharmacy of the St. Antonius Hospital in Nieuwegein, Mediq Apotheek Wassenaar, De Loosdrechtse Apotheek, and the outpatient pharmacy of the Amphia Hospital in Breda. In the Amphia Hospital she initiated the project "medication verification at discharge." Lenneke finished the education program of the Royal Dutch Pharmacists Association (KNMP) to become a specialist community pharmacist in 2013.

Next to her work as a pharmacist, in 2014 Lenneke started as a teacher at Utrecht University, division of Pharmacoepidemiology and Clinical Pharmacology. In 2015, she was selected for a PhD position. She started a tenure track, which was divided equally between teaching and performing research.

In her role as a teacher, Lenneke was involved in several activities, including teaching and supervising bachelor and master students, as well as being the coordinator and examiner of a master's course. She was involved in the development of the new Pharmacy curriculum in 2016 and is still responsible for developing and maintaining educational material in the master program. In addition, Lenneke is a member of the Teacher development team of the Department of Pharmaceutical Sciences and of the learning line "pharmacotherapeutic patient care" of the master program. She obtained her University Teaching Qualification in 2016.

Lenneke started her PhD research under supervision of Toine Egberts, Rob Heerdink, and Els van den Ban. Her research was focused on monitoring for adverse drug reactions in children and adolescents treated with antipsychotic drugs. Lenneke presented her work at national and international conferences.

Lenneke currently lives in Utrecht with her husband Tim and their twins Gijs and Walt. After completing her PhD thesis, she will continue working at Utrecht University.