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

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TITLE PAGE

Title

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

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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.

Setting

Guidelines from different countries were selected, and monitoring instructions for 13 ADR-related parameters were assessed.

Primary and secondary outcome measures

To assess the clarity and the applicability of the sections concerning monitoring instructions in each CPG, the Appraisal of Guidelines for Research and Evaluation (AGREE) instrument was used. To assess the clarity and the applicability of the monitoring instructions for each ADR-related parameter, the Systematic Information for Monitoring (SIM) 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 eight 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%).

Conclusions

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.

Keywords

Adverse effects, Antipsychotic agents, Child, Drug monitoring, Guideline

ARTICLE SUMMARY

Strengths and limitations of this study

- To the best of our knowledge, this is the first study that assessed the clarity and applicability of adverse drug reaction-related monitoring instructions in guidelines for children and adolescents treated with antipsychotic drugs.
- The AGREE-instrument and SIM-scores were used to assess the content and quality of the monitoring instructions in the clinical practice guidelines.
- Scoring was performed by two reviewers independently, and discrepancies were discussed and resolved by consensus.
- Scoring of the clinical practice guidelines and individual monitoring instructions remains partly subjective.
- By assessing the clinical practice guidelines, it becomes clear whether and on which topics these clinical practice guidelines need to be improved for the use in daily clinical practice.

INTRODUCTION

Antipsychotic drugs are widely prescribed on- 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, HbA1c, lipids, and prolactin), and observational (extrapyramidal and prolactin-related, e.g., 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 (Supplementary 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, JA, and EH) 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. 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 (e.g., parkinsonism and akathisia) and prolactin-related symptoms (e.g., gynecomastia, galactorrhoea, 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:

4. 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.

5. 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.

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

1. Clinical applicability
   - Evidence

- Applicability to target users
- Applicability to patients/populations

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

3. 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 (Supplementary 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 (JA 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 (Supplementary 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 1A). 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 (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 to 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, but 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 1B). 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 Canadian 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. Scoring of clinical practice guidelines according to the specific items of domains of the Appraisal of Guidelines Research and Evaluation (AGREE) instrument

Table 1A. 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	

WCHN: Women's and Children's Health Network; 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; AACAP: American Academy of Child and Adolescent Psychiatry.

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.

Table 1B. AGREE-REX

Clinical Practice Guideline	Country	Clinical applicability [c] 1.1	1.2	1.3	AGREE Score (%)	Values and preferences [d] 2.1	2.2	AGREE Score (%)	Implementability [e] 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	

REX: Recommendations Excellence.

WCHN: Women's and Children's Health Network; 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; AACAP: American Academy of Child and Adolescent Psychiatry.

Items AGREE-REX:

c. 1.1 Evidence; 1.2 Applicability to target users; 1.3 Applicability to patients/populations.

d. 2.1 Values and preferences of target users; 2.2 Values and preferences of patients/populations.

e. 3.1 Purpose; 3.2 Local application and adoption.

Monitoring instructions

The number of ADR-related parameters included in the CPGs varied between eight (the Netherlands) and 13 (Germany; Tables 2A and 2B). Monitoring instructions for the parameters weight, BMI, blood glucose, lipids, and prolactin were included in all CPGs (Table 2A). Monitoring instructions for the physical parameters pulse and the performance of an ECG were most often missing, namely in 50% (*n*=3) of the CPGs. Although the Canadian 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 and HbA1c were missing in 33.3% (*n*=2) of the CPGs, and monitoring instructions for height, blood pressure, and the two observational parameters extrapyramidal symptoms and prolactin-related symptoms were missing in 16.7% (*n*=1) of the CPGs. All CPGs described 'why to monitor' by explaining the ADRs that could be caused by antipsychotic drugs.

Although the Dutch 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 2B). For two CPGs, 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 did not clearly spell out when to stop monitoring, while the other two CPGs 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 one 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 (overall mean percentage: 68.7%), and how to respond if there were abnormalities in test results was not described for most parameters in these three CPGs (58.0%).

Table 2. Scoring of monitoring instructions according to the Systematic Information for Monitoring (SIM) score

Table 2A. Scoring of monitoring instructions for each adverse drug reaction-related parameter

	WCHN Australia	CAMESA Canada	DGPPN Germany	Accare The Netherlands	NICE United Kingdom	AACAP 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

WCHN: Women's and Children's Health Network; 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; AACAP: American Academy of Child and Adolescent Psychiatry.

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.

Table 2B. 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

WCHN: Women's and Children's Health Network; 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; AACAP: American Academy of Child and Adolescent Psychiatry.

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, HbA1c, 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'.

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 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 Canadian 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 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,[27] while a study by Mangurian at el. has shown that a large proportion of the primary care providers seem to be unaware of the consensus guidelines.[30] Nevertheless, previous studies have demonstrated that monitoring rates were low and remained low after implementation of monitoring guidelines.[12,14] 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 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.

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.

DECLARATIONS

Authors' contributions

All authors contributed to the study conception and design. Data collection and analysis were performed by Lenneke Minjon, Juul W. Aarts, and Eibert R. Heerdink. Final inconsistencies were discussed with all authors until consensus was reached. The first draft of the manuscript was written by Lenneke Minjon and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Competing interests

None declared.

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Data availability statement

The guidelines included in this study are freely available on the internet.

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Not applicable.

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Ethics approval

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SUPPLEMENTAL MATERIAL

Supplementary 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

Supplementary 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 paediatrician 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

Ferner RE, Coleman J, Pirmohamed M, et al. The quality of information on monitoring for haematological adverse drug reactions. Br J Clin Pharmacol 2005;60:448–51. doi:10.1111/j.1365-2125.2005.02440.x

Supplementary 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

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Secondary Subject Heading:	Mental health
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TITLE PAGE

Title

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.

Setting

Guidelines from different countries were selected, and monitoring instructions for 13 ADR-related parameters were assessed.

Primary and secondary outcome measures

To assess the clarity and the applicability of the sections concerning monitoring instructions in each CPG, the Appraisal of Guidelines for Research and Evaluation (AGREE) instrument was used. To assess the clarity and the applicability of the monitoring instructions for each ADR-related parameter, the Systematic Information for Monitoring (SIM) 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 eight 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%).

Conclusions

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.

Keywords

Adverse effects, Antipsychotic agents, Child, Drug monitoring, Guideline

Strengths and limitations of this study

- To the best of our knowledge, this is the first study that assessed the clarity and applicability of adverse drug reaction-related monitoring instructions in guidelines for children and adolescents treated with antipsychotic drugs.
- The AGREE-instrument and SIM-scores were used to assess the content and quality of the monitoring instructions in the clinical practice guidelines.
- Scoring was performed by two reviewers independently, and discrepancies were discussed and resolved by consensus.
- Scoring of the clinical practice guidelines and individual monitoring instructions remains partly subjective.
- By assessing the clinical practice guidelines, it becomes clear whether and on which topics these clinical practice guidelines need to be improved for the use in daily clinical practice.

INTRODUCTION

Antipsychotic drugs are widely prescribed on- 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, HbA1c, lipids, and prolactin), and observational (extrapyramidal and prolactin-related, e.g., 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 (Supplementary 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, JA, and EH) 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 (e.g., parkinsonism and akathisia) and prolactin-related symptoms (e.g., gynecomastia, galactorrhoea, 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:

4. 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.

5. 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:

I. Clinical applicability

- Evidence

- Applicability to target users
- Applicability to patients/populations

II. Values and preferences

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

III. 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 (Supplementary 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 (JA 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 (Supplementary 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 1A). 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 (WCHN, NICE and 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 to 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 1B). 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 CAMESAguideline 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. Scoring of clinical practice guidelines according to the specific items of domains of the Appraisal of Guidelines Research and Evaluation (AGREE) instrument

Table 1A. 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	

WCHN: Women's and Children's Health Network; 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; AACAP: American Academy of Child and Adolescent Psychiatry.

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.

Table 1B. AGREE-REX

Clinical Practice Guideline	Country	Clinical applicability [c] 1.1	1.2	1.3	AGREE Score (%)	Values and preferences [d] 2.1	2.2	AGREE Score (%)	Implementability [e] 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	

REX: Recommendations Excellence.

WCHN: Women's and Children's Health Network; 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; AACAP: American Academy of Child and Adolescent Psychiatry.

Items AGREE-REX:

c. 1.1 Evidence; 1.2 Applicability to target users; 1.3 Applicability to patients/populations.

d. 2.1 Values and preferences of target users; 2.2 Values and preferences of patients/populations.

e. 3.1 Purpose; 3.2 Local application and adoption.

Monitoring instructions

The number of ADR-related parameters included in the CPGs varied between eight (Accare) and 13 (DGPPN; Tables 2A and 2B). Monitoring instructions for the parameters weight, BMI, blood glucose, lipids, and prolactin were included in all CPGs (Table 2A). 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 2 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 1 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 2B). 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 one 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 2. Scoring of monitoring instructions according to the Systematic Information for Monitoring (SIM) score

Table 2A. Scoring of monitoring instructions for each adverse drug reaction-related parameter

	WCHN Australia	CAMESA Canada	DGPPN Germany	Accare The Netherlands	NICE United Kingdom	AACAP 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

WCHN: Women's and Children's Health Network; 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; AACAP: American Academy of Child and Adolescent Psychiatry.

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.

Table 2B. 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

WCHN: Women's and Children's Health Network; 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; AACAP: American Academy of Child and Adolescent Psychiatry.

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, HbA1c, 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'.

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,[27] while a study by Mangurian at el. has shown that a large proportion of the primary care providers seem to be unaware of the consensus guidelines.[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 6 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.

DECLARATIONS

Authors' contributions

LM, JWA, EvdB, TCGE and ERH contributed to the plan and design of the study. LM, JWA and ERH analysed the data. LM drafted the manuscript and was in charge of study planning. LM, JWA, EvdB, TCGE and ERH contributed to the interpretation of the results and critical revision of the manuscript for important intellectual content and approved the final version of the manuscript. LM and ERH are the guarantors of this paper.

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The guidelines included in this study are freely available on the internet.

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Not applicable.

Ethics approval

Not applicable.

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SUPPLEMENTAL MATERIAL

Supplementary 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

Supplementary 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 paediatrician 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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Supplementary 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