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Guideline Adherence of Monitoring Antipsychotic Use for Nonpsychotic Indications in Children and Adolescents

A Patient Record Review

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Abstract:

Background: Antipsychotics are frequently prescribed to children and adolescents for nonpsychotic indications. Guidelines recommend regularly assessing treatment response and adverse effects and the ongoing need for their use. We aimed to assess adherence to recommendations of available guidelines regarding monitoring antipsychotic use and to test the influence of children's age, sex, intelligence quotient, and diagnosis on adherence.

Methods: We reviewed 426 medical records from 26 centers within 3 large Dutch child and adolescent psychiatry organizations, excluding children with schizophrenia, psychosis, mania, or an intelligence quotient below 70. We investigated whether there was regular assessment of treatment response, adverse events (physical and laboratory), and at least annual discussion of the need of continued use.

Results: On average, treatment response was assessed in 69.3% of the recommended treatment periods, height in 25.6%, weight in 30.6%, blood pressure in 20.6%, evaluation of adverse events in 19.4%, and cardiometabolic measures in 13.7%; discontinuation and/or continued need was discussed at least annually in 36.2%. Extrapyramidal and prolactin-related adverse effects, waist circumference, glucose, and lipids were rarely investigated. Higher age was associated with lower rates of assessment of treatment response. Most antipsychotics were prescribed long-term. In those children with sufficient documentation of the course of treatment, 57.7% was still using an antipsychotic 3 years after initiation.

Conclusions: Our findings indicate insufficient adherence to guideline recommendations for monitoring antipsychotic use in children and adolescents, as well as long duration of use in the majority of children. Especially, older children are at higher risk of receiving suboptimal care.

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In the past decades, antipsychotic use has become widespread in child and adolescent psychiatry, mostly for nonpsychotic indications. However, adverse effects such as weight gain, increased prolactin levels, development of diabetes, and extrapyramidal symptoms often accompany this use,[1] and children and adolescents are more at risk of developing them.[2] Therefore, appropriate monitoring of possible adverse drug reactions and mitigating adverse events once they have started to occur is of great importance in clinical practice.[3,4]

Available guidelines aimed at the use of antipsychotics in children and adolescents[5–15] stress the importance of doing assessments before initiating antipsychotics and following up regularly and systematically, which should include a review of treatment response, extrapyramidal and prolactin-related adverse effects, and reviewing various cardiometabolic parameters, such as length, weight, waist circumference, blood pressure, pulse, and glucose and lipid levels. Importantly, several guidelines also recommend regular evaluation of the continued need of the antipsychotic treatment for nonpsychotic indications, as stated by the American Academy of Child Adolescent Psychiatry: "In clinical practice, medications are often continued for years, and while this may be appropriate in specific cases, the indefinite use of atypical antipsychotics should not be assumed. Regular assessments of the continued need for the atypical antipsychotic should be done."[5] It is unclear to what extent children and adolescents being treated with antipsychotics in clinical practice are monitored in line with these guidelines.

Adherence to monitoring metabolic adverse events has received most attention in previous studies. By reviewing medical records,[16–24] consulting insurance claim or pharmacy databases,[25–32] or by conducting surveys among prescribers,[33–37] varying rates of metabolic monitoring have been reported. Height, weight, and blood pressure are generally well monitored, but especially, testing of glucose and lipid levels was found to be infrequent. Other aspects of monitoring, such as rates of monitoring of treatment response, extrapyramidal side effects, prolactin-related adverse effects, and rates of discussion of continued need have not been studied as extensively. Although some studies have included some of these aspects as well,[33,34,36] their full reliance on self-reported monitoring behaviors make these studies prone to bias. So far, only 2 studies have evaluated monitoring guideline adherence by retrospective record review, but both were aimed at children with intellectual disabilities.[38,39] Although data from insurance claims or pharmacy databases are probably most reliable, not all relevant aspects of monitoring guideline adherence can be derived from such databases.

Therefore, we conducted a medical record review investigating a comprehensive set of recommendations for initiating and monitoring antipsychotic use in children and adolescents without intellectual disabilities. We studied the rates of (1) assessing treatment response, (2) monitoring adverse events, (3) cardiometabolic monitoring, and (4) discussion of continued need and discontinuation. Furthermore, we aimed to explore the association of children's age, sex, intelligence quotient (IQ), and psychiatric diagnosis on adherence to guideline recommendations.

MATERIALS AND METHODS

Sample

We reviewed 426 randomly selected medical records from 3 organizations for child and adolescent psychiatry in the Netherlands that offer both inpatient and outpatient treatment. We screened medical records from randomized lists of patients who had received an antipsychotic prescription in 2012 or had had an appointment for psychopharmacological treatment in that year and reviewed them if inclusion criteria were met. Our previous article contains full details regarding data collection.[40] Inclusion criteria were patients (1) receiving a prescription for an antipsychotic agent in 2012 (ensuring that at least 3 years of treatment could be reviewed); (2) receiving their first antipsychotic prescription at the center where the record was included; (3) 17 years or younger at the time of the first prescription; (4) not having a diagnosis of schizophrenia, psychosis, or mania; and (5) not having an intellectual disability (ie, total IQ of 70 or above) or, if IQ was unknown, attending regular level education.

Measure

Table 1 displays the guideline recommendations that were evaluated in this study, as well as the recommended monitoring schedule for each parameter and the corresponding time intervals. We selected those guideline recommendations that were mentioned by at least half of the guidelines on monitoring of antipsychotics in children and adolescents that were available in 2012 and published in either English or Dutch.[5–12,14,41–43] Recommended monitoring frequencies for physical and laboratory measures varied somewhat across guidelines; therefore, we determined the lowest acceptable monitoring frequency for each parameter. We only selected adherence to recommendations that were relevant for children using antipsychotics in general, that is, excluded were those that are only recommended when indicated by the use of a specific type of antipsychotic or the presence of risk factors in the patient or family history.

Some parameters are only recommended to be monitored regularly. For those, we checked whether monitoring had occurred in the first 3 months, between 3 and 6 months, and every 6 months thereafter until a maximum of 3 years after the antipsychotic prescription (Table 1). All mentions of a discontinuation or dose reduction to eventually discontinue, both initiated by the clinician and the child or parents, were considered an attempt at discontinuation.

In addition, for each patient, we recorded age at the time of the first prescription, sex, total IQ, and psychiatric diagnoses as reported in the record before the first antipsychotic prescription. For this, we categorized children who received a diagnosis of autism spectrum disorder (ASD; irrespective of comorbidity), attention-deficit/hyperactivity disorder (irrespective of comorbidity but without ASD), or disruptive behavior disorder (without ASD or attention-deficit/hyperactivity disorder), according to the hierarchy of diagnoses used in the *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition) (*DSM-IV*). In addition, we distinguished a group of children with other *DSM-IV* diagnoses and a group of children who had no recorded psychiatric diagnosis in their medical record. Furthermore, for those records in which the course of the antipsychotic use was well documented, we calculated the number of days on which an antipsychotic was used during the first 3 years after the first prescription, as well as the number of attempted stops.

Procedure

The study was conducted between January 2016 and June 2017. Five research assistants with a master's degree in either psychology or a related field were extensively trained to screen and review the patient records. These assistants had regular meetings to reach consensus on how to rate specific cases. If they could not agree, M.D. made the decision, after deliberating with B.J.v. d.H. when necessary.

For each included medical record, we reviewed all instances during which 1 or more parameters mentioned in Table 1 were assessed by a psychiatrist, physician, or nurse practitioner that were reported in the record up to 3 years after the first antipsychotic prescription, until the antipsychotic was discontinued for at least 1

TABLE 1. Guideline Recommendations Regarding the Monitoring of Antipsychotic Use in Children and Adolescents, Lowest Recommended Frequencies of Monitoring and Time Intervals That Were Evaluated in This Study for Each Parameter

Guideline Recommendation	Parameter	Recommended Monitoring Schedule
1. Regularly assess treatment response	Monitoring of treatment response	Regularly
2. Regularly assess adverse events	Monitoring of extrapyramidal adverse effects	Regularly
	Monitoring of prolactin-related adverse effects	Regularly
	Monitoring of other adverse effects	Regularly
3. Regularly perform cardiometabolic monitoring	Measurement of height	Baseline, 4 wk, 8 wk, 12 wk, annually
	Measurement of weight	Baseline, 4 wk, 8 wk, 12 wk, annually
	Measurement of waist circumference	Baseline, annually
	Measurement of blood pressure	Baseline, 12 wk, annually
	Measurement of pulse	Baseline, 12 wk, annually
	Measurement of glucose levels	Baseline, 12 wk, annually
	Measurement of lipid profile	Baseline, 12 wk, annually
4. Regularly evaluate continued need of antipsychotics use and consider discontinuation	Discussion of continued need of antipsychotic use (regardless of actual discontinuation)	No schedule recommended, but operationalized in our study as at least annually

month, or until the patient was transferred to another center or to the care of a general practitioner. For determining the number of days of antipsychotic use, we also evaluated use after a period of discontinuation of 1 month or longer, but we excluded patients in which exact dates were unclear, for example, when the time range in which a change in antipsychotic use occurred was longer than 1 month (eg, "summer of 2012," "between January and April").

Data Analysis

To answer whether guideline adherence was related to children's age, sex, IQ, or diagnosis, we calculated an overall guideline adherence score for each patient on each recommendation on a scale from 0 to 100. For that, we calculated the proportion of adhered time intervals per parameter and averaged these across recommendations. Analyses were done separately for each recommendation.

Multiple regression was used to assess the predictive value of age, sex, and IQ on the total guideline adherence scores. All analyses were corrected for the duration of antipsychotic use that was reviewed by adding this as a predictor, because this was strongly associated with several of the other predictors (age, $r_{421} = -0.265$ [$P < 0.001$]; sex, $T_{420} = 2.15$ [$P = 0.032$]). We analyzed differences between diagnostic groups using 1-way analyses of variance (ANOVAs), but because of large heterogeneity in diagnoses in the *other DSM-IV diagnoses group* and a low sample size in the *no diagnosis group*, we excluded these from the ANOVAs.

RESULTS

We reviewed a total of 426 medical records, which included n = 49 from one organization and n = 190 and n = 187 from the others, distributed across 26 centers in total. Patient characteristics are described in Table 2. The average total IQ was 95.2 (SD, 15.8). Four patients (0.9%) received a prescription for an antipsychotic but never started taking it. These patients were included in baseline statistics but excluded from further analyses. Five patients (1.2%) did not start taking the antipsychotic immediately after getting the prescription. The average time between prescription and antipsychotic start for this group was 101 days (SD, 142 days; range, 26–353 days). Antipsychotic use was reviewed for an average of 767 days (SD, 422 days; range, 2–1096 days) until discontinuation during at least 1 month (n = 158), transfer to another center or a general practitioner (n = 27), or until the maximum period of 3 years (n = 242).

Guideline Adherence

Although treatment response was adequately monitored in the majority of patients (adherence ranged from 58.0% to 80.3% in the evaluated time intervals), adherence to recommendations regarding height (adherence ranged from 11.0% to 46%), weight (14.8%–52.6%), blood pressure (10.2%–38.3%), and pulse (6.3%–38.3%) was considerably lower. Other parameters were even less frequently monitored, with adherence rates below 10%, whereas prolactin-related adverse effects, measurement of waist circumference, and glucose and lipid profiles were hardly ever assessed. For 29 patients (6.9%), it was reported that additional physical measures were done outside of the center. These measurements were not reported in the medical record and were not included in our analyses. Frequencies of monitoring of each parameter in the recommended time intervals can be found in the table in Supplemental Digital Content 1, http://links.lww.com/JCP/A710.

Table 3 shows the total adherence scores for each of the guideline recommendations, as well as the separate parameter scores that were used to calculate these scores. Adherence was highest for the regular reviewing of treatment response and lowest for cardiometabolic monitoring, although adherence scores per parameter in the latter varied substantially.

TABLE 2. Patient Characteristics at the Time of the First Antipsychotic Prescription: Age, Sex, Intellectual Functioning, Primary Psychiatric Diagnosis, Type of Antipsychotic That Was Initially Prescribed, and the Duration of Antipsychotic Treatment That Was Reviewed to Evaluate Guideline Adherence

	Total Sample (n = 426)
Age, mean (SD) (range), y	10.1 (3.36) (3.33–18.0)
Sex, n (%)	
Male	327 (76.8)
Female	99 (23.2)
Intellectual functioning, n (%)	
Borderline (TIQ = 70–79)	58 (13.6)
Low average (TIQ = 80–89)	92 (21.6)
Average (TIQ = 90–109)	123 (28.9)
High average (TIQ = 110–119)	39 (9.2)
Superior (TIQ = 120–129)	27 (6.3)
Very superior (TIQ, > 129)	5 (1.2)
Not reported	82 (19.2)
Primary *DSM-IV* axis I diagnosis, n (%)	
Autism spectrum disorder	228 (53.5)
Attention-deficit/hyperactivity disorder	81 (19.0)
Disruptive behavior disorder	21 (4.9)
Other *DSM-IV* diagnoses*	67 (15.7)
No diagnosis	29 (6.8)
Antipsychotic, n (%)	
Risperidone	293 (68.8)
Pipamperone	46 (10.8)
Aripiprazole	39 (9.2)
Olanzapine	28 (6.6)
Haloperidol	8 (1.9)
Quetiapine	6 (1.4)
Pimozide	1 (0.2)
Trial with multiple types of antipsychotics	2 (0.5)
Type of antipsychotic not reported	3 (0.7)
Duration of reviewed antipsychotic treatment, n (%)	
0 wk†	25 (5.9)
6 wk	18 (4.2)
10 wk	15 (3.5)
3 mo	30 (7.0)
6 mo	47 (11.0)
12 mo	28 (6.6)
18 mo	14 (3.3)
24 mo	21 (4.9)
30 mo	12 (2.8)
36 mo	212 (49.8)
Never started taking an antipsychotic after their prescription	4 (0.9)

*This category includes all axis I diagnoses mentioned in the *DSM-IV*.

†These patients used an antipsychotic fewer than 6 weeks. Adherence was only calculated for time intervals during which the antipsychotic was used continuously. Only baseline measures were used to calculate adherence scores for these patients.

TIQ indicates total intelligence quotient.

TABLE 3. Total Adherence Score for Each Guideline Recommendation and Adherence Scores for Each Parameter That Was Used to Calculate the Total Adherence Scores

Guideline Recommendation	Total Guideline Adherence Score, Mean (SD)*	Evaluated Parameters	Parameter Adherence Score, Mean (SD)*
1. Regularly assess treatment response	69.3 (31.5)		
2. Regularly assess adverse events	19.4 (14.2)	Monitoring of extrapyramidal adverse effects	7.4 (17.1)
		Monitoring of prolactin-related adverse effects	0.6 (3.7)
		Monitoring of other adverse effects	50.3 (33.4)
3. Regularly perform cardiometabolic monitoring	13.7 (12.8)	Measurement of height	25.6 (26.0)
		Measurement of weight	30.6 (27.1)
		Measurement of waist circumference	0.12 (2.4)
		Measurement of blood pressure	23.1 (30.1)
		Measurement of pulse	13.6 (23.5)
		Measurement of glucose levels	1.5 (8.5)
		Measurement of lipid profile	1.2 (7.7)
4. Regularly evaluate continued need of antipsychotics use and consider discontinuation	36.2 (48.1)		

*Equals the mean value of the adherence on corresponding parameters, range of 0 to 100.

†Equals the number of time intervals in which the parameter was monitored, divided by the number of time intervals during which the patient used the antipsychotic the entire time, multiplied by 100, range of 0 to 100.

Predictors of Adherence

Regression analyses investigating the associations with children's age, sex, and IQ on the 4 guideline recommendation adherence scores indicated that age had a significant effect on adherence. That is, a higher age was associated with a lower score on regularly reviewing medication response ($P < 0.001$, $\beta = -0.21$). The ANOVAs with which we analyzed the predictive effects of psychiatric diagnoses yielded nonsignificant results. Full details on the regression analyses results can be found in Supplemental Digital Content 2, http://links.lww.com/JCP/A711.

Duration of Antipsychotic Use

The course of antipsychotic treatment during the first 3 years after the first prescription was sufficiently documented to calculate duration of use in 317 patients (75.1%) of the 422 who started taking the antipsychotic. Of these 317 patients, 183 (57.7%) used an antipsychotic beyond 3 years after the first prescription, using an antipsychotic for 1059.5 days on average when stops were excluded. Those patients who discontinued the antipsychotic use during these 3 years (n = 103, 32.5%) did so 455.7 days on average after their first prescription, of which they used an antipsychotic for 378.5 days. For the other 31 patients (9.8%), care was transferred to another organization or to their general practitioner, so we were unable to evaluate duration of use in this group. In 76 (24.0%) of the 317 medical records at least 1 antipsychotic stop was documented. In this group, the average amount of stops was 1.26 (SD, 0.55) per patient, and the average total duration of these stops was 152 days. All details on duration of use and stops can be found in Supplemental Digital Content 3, http://links.lww.com/JCP/A712.

DISCUSSION

Through this retrospective medical record review, we found generally low guideline adherence regarding the monitoring of antipsychotic use in children and adolescents. Although treatment response was relatively well monitored and physical parameters such as height, weight, and blood pressure were relatively well monitored, monitoring of extrapyramidal adverse effects, prolactin-related adverse effects, waist circumference, glucose, and lipid profile were documented in only a small number of patients. Also, discontinuation and the discussion of continued need were only adequately done in about 30% of our sample. Higher age was associated with lower rates of reviewing treatment response. This indicates that especially older children are at risk for suboptimal treatment and unwarranted long-term use without regular reassessments.

Our findings are generally in line with those found by previous studies, with generally low monitoring of glucose and lipid profiles, and more adequate monitoring of weight and blood pressure, although there was still room for improvement.[16,19,26] Self-reported monitoring rates have been found to be higher,[34–36] but this could reflect socially desirable responding of prescribing clinicians in these studies. Our findings indicate that laboratory assessments are often omitted, which is undesirable because of the risk of developing metabolic conditions such as diabetes, because of not catching any abnormalities in time.

Also of interest are our findings regarding the duration of antipsychotic treatment. On average, use in our sample was long term, and only a minority of medical records mentioned stops during antipsychotic use. Although antipsychotics are only indicated for short-term use,[44–47] most guidelines that were available in 2012 did not mention a maximum time of treatment with an antipsychotic or frequencies in which discontinuation should be discussed or attempted. Some do mention the need to evaluate continued need after 6 to 12 months.[6,14] One of the newer guidelines, the Dutch guideline for oppositional behavioral disorders from 2013,[48] recommends a treatment period of three to a maximum of 6 months. Although it would be unfair to compare our sample to these newer standards, even our rather conservative standard of annual consideration of discontinuation was only met in a little over a third of the cases.

Compared with previous studies, the current study has some important strengths. For example, we did not rely on monitoring behaviors as reported by the prescribing clinicians, which

prevented socially desirable outcomes. Furthermore, we comprehensively studied antipsychotic monitoring, including all of the most important monitoring parameters mentioned by relevant guidelines in a large sample from 26 both inpatient and outpatient centers from 3 large organizations for child and adolescent psychiatry, which is representative for child and adolescent psychiatric care in the Netherlands.

However, relying solely on medical records in some cases proved to be a disadvantage as well because information may have been missing in the medical records, especially in older ones. Also of interest, for a number of patients, it was indicated that monitoring was partly done outside the center. For example, a number of patients lived in a group home where they were weighed regularly or went to a pediatrician outside the center to be checked. Although the results of these assessments were not reported in the medical record, the fact that they were monitored may have negatively influenced the monitoring rates in our study. Furthermore, there are some methodological factors that may have affected our results. First, the time windows we selected to review for the cardiometabolic adverse effects were relatively narrow, excluding some of the monitoring that was done outside of these windows. Second, because we reviewed the 3 years after the first antipsychotic prescription, for those patients who were prescribed with an antipsychotic but started later than the date of the first prescription, antipsychotic use was not reviewed for 3 years.

Future studies could investigate the effects of characteristics of organizations (eg, presence of laboratory facilities and of internal medication guidelines), clinicians (eg, years of experience, attitudes toward use of psychotropic medication), or additional patient factors (eg, ethnicity, reluctance to blood draw or nonadherence to laboratory orders) on the adherence to antipsychotic monitoring guidelines. It could also be informative to compare guideline adherence in on-label versus off-label users or to investigate predictors of duration of use. Future studies should furthermore aim to find ways to facilitate proper monitoring, such as developing electronic aids supporting regular and thorough monitoring as well as reminders to discuss the possibility of discontinuation. This treatment optimization could protect patients from unwarranted long-term use and the possibility of developing more severe long-term adverse effects of antipsychotic use. It could also help clinicians to be critical when prescribing antipsychotic agents and keep striving toward finding what treatment works best, with the least risk of unwanted effects for each individual patient.

In conclusion, our study confirms findings from previous studies indicating that antipsychotic monitoring in children and adolescents should be improved on a number of points and that, although antipsychotics are only indicated for short term use, they are often prescribed for long periods. In particular, the monitoring of extrapyramidal and prolactin-related adverse effects, metabolic laboratory measures, and the assessment of continued need of antipsychotic use should receive more regular attention during the course of antipsychotic treatment. The challenge lies in finding ways to improve monitoring practices of clinicians, but education on proper monitoring according to guidelines or implementing a monitoring checklist in electronic medical records may have positive effects on monitoring rates.[20,21,49] Further interventions to optimize guideline adherence could consider restrictions to continued prescribing if guidelines are not being followed. However, increasing awareness of current gaps in monitoring practices in prescribing clinicians is an essential first step.

AUTHOR DISCLOSURE INFORMATION

J.K.B. has been in the past 3 years a consultant to, member of advisory board of, and/or speaker for Janssen Cilag BV, Eli Lilly, Lundbeck, Takeda/Shire, Roche, Medice, and Servier. He is not an employee of any of these companies and not a stock shareholder of any of these companies. He has no other financial or material support, including expert testimony, patents, and royalties. The other authors have no conflicts of interest relevant to this article to disclose. This study was funded by The Netherlands Organization for Health Research and Development (ZonMW; grant number 836021020).

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