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Brief Report

Impact of Antipsychotic Guidelines on Laboratory Monitoring in Children with Neurodevelopmental Disorders

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Abstract

Objectives: The Canadian Alliance for Monitoring Effectiveness and Safety of Antipsychotics in Children (CAMESA) guidelines provide monitoring recommendations for children who are treated with second-generation antipsychotics (SGAs). The objective of this study was to determine the impact of the CAMESA guidelines on SGA monitoring in children with neurodevelopmental disorders.

Methods: A retrospective chart review compared laboratory monitoring in children treated with SGAs who were referred to a tertiary psychopharmacology clinic before (2008–2011) and after (2013–2016) CAMESA publication. Chi-squared tests were used to detect changes in SGA use and monitoring between the two time periods.

Results: A total of 345 charts were reviewed ($n = 136$ pre-CAMESA, $n = 209$ post-CAMESA). The proportion of children taking an SGA increased significantly (35% vs. 49%; $p = 0.02$) as did the duration of SGA treatment before tertiary assessment (18.6 months vs. 27.2 months; $p = 0.03$). SGA monitoring data were missing in 40% of charts pre-CAMESA and in 31% of charts post-CAMESA. The proportion of patients with any available laboratory monitoring did not change between the time periods (35% pre-CAMESA vs. 39% post-CAMESA; $p = 0.56$). Similarly, the proportion of patients with full laboratory monitoring was not significantly different between time periods (15% pre-CAMESA vs. 25% post-CAMESA; $p = 0.23$).

Conclusions: SGA monitoring rates did not significantly improve after CAMESA guideline publication. To maximize benefit and mitigate risks of these medications, there is a need to identify barriers to SGA monitoring.

Keywords: child development disorders, autism spectrum disorders, autism, antipsychotics, psychotropic drugs

Introduction

The use of second-generation antipsychotic (SGA) medications has increased over the past two decades (Harrison et al. 2012; Zito et al. 2013). One group of children with relatively high SGA prescription rates are those with neurodevelopmental disorders (NDDs). Aripiprazole and risperidone are two Food and Drug Administration-approved SGAs used to treat irritability and aggression in children with autism spectrum disorder (ASD), with several trials demonstrating their efficacy (Accardo 2003; Marcus et al. 2009; Owen et al. 2009). A meta-analysis of 39 studies revealed that ~1 in 10 children treated with antipsychotic medications had a diagnosis of ASD and/or intellectual disability (ID) (Park et al. 2016). The analysis concluded that the proportion of antipsychotic-treated children with a diagnosis of ASD and/or ID grew between 1996 and 2011.

Children taking SGAs are at risk for adverse effects. A study of first-time SGA use in children revealed an average weight gain ranging from 1.61 kg (aripiprazole) to 4.52 kg (olanzapine) after 4 weeks, with continued weight gain at 12 weeks (Correll et al. 2009). Studies have also demonstrated elevated blood glucose and up to a threefold increased risk of diabetes in pediatric patients treated with SGAs (Bobo et al. 2013). SGAs have been associated with elevated lipid profiles and blood pressure in children, which, in addition to poor glycemic control, predict adult cardiovascular risk (Correll et al. 2009; Panagiotopoulos et al. 2010). Although SGAs have a lower risk of extrapyramidal side effects than first-generation antipsychotics, these risks still exist, particularly with risperidone and aripiprazole (Pringsheim et al. 2011a). Finally, a recent retrospective cohort study revealed an increase in rates of unexpected death in children taking antipsychotic medications compared with controls (Ray et al. 2019).

In 2011, the Canadian Alliance for Monitoring Effectiveness and Safety of Antipsychotics in Children (CAMESA) published clinical and laboratory monitoring guidelines to promote safe

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antipsychotic use in children (Pringsheim et al. 2011b). These recommendations involve monitoring growth parameters, blood pressure, and laboratory measures at specific time points. A recent study from Alberta, Canada, revealed that rates of pediatric SGA laboratory monitoring ranged between 17% and 42% in 2014, 3 years after CAMESA guideline publication (Chen et al. 2018). Two similar studies also demonstrated inconsistent adherence to the CAMESA guidelines (Coughlin et al. 2018; Javaheri and McLennan 2019). At present, there are no studies comparing monitoring rates before and after publication of pediatric SGA guidelines.

The primary objective of this study was to evaluate whether CAMESA guideline publication improved SGA laboratory monitoring rates in children with NDDs. We also aimed to characterize the clinical management of children with NDDs, including the number and type of psychoactive medications trialed before assessment in a tertiary psychopharmacology clinic.

Methods

This was a retrospective cohort study of children with NDDs who were referred to a psychopharmacology clinic at a children's rehabilitation hospital. The clinic accepts referrals of children with NDDs who have failed to achieve optimal management on at least one medication.

All charts of children who were newly assessed in the clinic before (2008–2011) and after (2013–2016) publication of the CAMESA guidelines were identified and reviewed. The post-publication time period was selected to allow sufficient time for guideline uptake.

Information including age, gender, growth parameters, NDD diagnoses, and reason for referral was collected from the referral letter. Body mass index (BMI) was calculated using weight and height measurements recorded in the clinic (WHO Multicentre Growth Reference Study Group 2006). Pharmacological management data were collected by documenting the number and type of medication(s) each child was taking at the time of the first clinic visit.

The charts of children treated with SGAs were further analyzed. Information regarding laboratory tests children had undergone before referral was gathered from either the referral letter or the clinic note. Children who had undergone laboratory investigations were divided into three categories: (1) any investigations complete, (2) no investigations complete, and (3) not specified. Children in the first category were further divided into (1) all investigations complete and (2) some investigations complete. ''All investigations'' were defined as blood glucose level and/or hemoglobin A1C, lipid profile, prolactin, aspartate transaminase, alanine transaminase, and prolactin as per the CAMESA guidelines. These tests and any abnormal values were recorded if documented in the referral letter and/or forwarded to the clinic.

Descriptive statistics were used to analyze demographic information and medications prescribed before first assessment in the clinic. A chi-squared test was used to compare the proportion of children prescribed SGAs in the pre- and post-CAMESA time periods. A Student's *t*-test was used to compare the duration of SGA therapy in the pre- and post-CAMESA time periods. Chi-squared tests were used to determine whether there were significant differences in rates of clinical monitoring before and after CAMESA publication, in the rates of reporting of SGA monitoring, and in the completeness of SGA monitoring. All statistical analyses were completed in R (R Core Team 2013).

Ethics approval was obtained from Holland Bloorview's research ethics board.

Results

A total of 345 charts were reviewed ($n = 136$ pre-CAMESA, $n = 209$ post-CAMESA). Characteristics of the sample are outlined in Table 1. Across time periods, the majority of children referred (87%) had an ASD diagnosis. The most common reason for referral in both time periods was aggression (54%). Attention-deficit/hyperactivity disorder (ADHD) diagnoses became more common in the post-CAMESA period (19% vs. 37% of referrals; $p < 0.001$), which may be due to the change in DSM-5 allowing concurrent diagnosis of ASD and ADHD (American Psychiatric Association 2013). The number of medications used by the time the child was seen in the clinic was significantly different between the two time periods, with relatively more children on three or more medications in the post-CAMESA period ($\chi^2 = 8.8$; $p = 0.03$). Across time periods, SGAs were the most commonly prescribed medication (42%), followed by stimulants (23%), selective serotonin reuptake inhibitors (16%), and clonidine/guanfacine (11%). A significantly higher proportion of referred children were treated with SGAs in the post-CAMESA period (49%) than the pre-CAMESA period (35%; $\chi^2 = 5.6$; $p = 0.02$).

Results for SGA monitoring are presented in Table 2. The mean SGA treatment duration was 18.6 months (standard deviation [SD] 14.7) in the pre-CAMESA cohort and 27.2 months (SD 24.6) in the post-CAMESA cohort, corresponding to a significant increase between the two time periods ($t = 2.2$, $p = 0.03$). In many cases, neither the referring physician nor the receiving physician in the clinic documented SGA monitoring. These data were missing for 19 patients treated with SGAs pre-CAMESA (40%) and for 32 patients treated with SGAs post-CAMESA (31%), a nonsignificant difference ($\chi^2 = 0.16$; $p = 0.69$).

Seventeen children (35%) in the pre-CAMESA period and 39 children (38%) in the post-CAMESA period underwent any laboratory testing. When including the three categories of any testing, no testing, and missing data, there were no significant differences between the pre- and post-CAMESA periods ($\chi^2 = 1.2$; $p = 0.56$). Seven children in the pre-CAMESA period (15%) and 26 (25%) children in the post-CAMESA period underwent full laboratory monitoring. When including full/partial/no testing and missing data, there were no significant differences between the pre- and post-CAMESA periods ($\chi^2 = 4.3$; $p = 0.23$). Of the available laboratory tests, 53% (9/17) in the pre-CAMESA time period and 28% (11/39) in the post-CAMESA time period were outside the range of normal ($\chi^2 = 2.2$; $p = 0.14$).

Discussion

This is the first study to examine whether the publication of pediatric SGA guidelines changed monitoring practices in children with NDDs. Unfortunately, we did not find a significant improvement after CAMESA guideline publication. Although SGAs can be an appropriate choice for some patients with NDDs, their use is not without risk. Approximately 40% of available laboratory tests in our study were abnormal, demonstrating that these adverse effects do exist. These abnormalities should inform clinical management by prompting important discussions between providers and patients regarding the risks and benefits of ongoing SGA use.

Our study also found high rates of SGA prescription among our sample of children with NDDs, including a significantly higher proportion of children who were treated with SGAs in the post-CAMESA period. We considered whether this may reflect a lower threshold to refer children treated with SGAs for tertiary management after guideline publication; however, when paired with the

Table 1. Patient Characteristics

	Compiled (n = *345*)	*All* (%)	*Pre-CAMESA* (n = *136*)	*Pre-CAMESA* (%)	*Post-CAMESA* (n = *209*)	*Post-CAMESA* (%)
Gender						
Male	284	82	111	82	173	83
Female	61	18	25	18	36	17
Age						
Mean (SD)	10.4 (3.59)		10.5 (3.95)		10.3 (3.34)	
Median	10		10		10	
Range	2–18		3–18		2–18	
BMI percentile						
0–25	71	21	28	21	43	21
26–50	39	11	16	12	23	11
51–75	43	12	12	9	31	15
76–99	84	24	44	32	40	19
Diagnosis						
ASD	299	87	115	85	184	88
ADHD**	103	30	26	19	77	37
Seizure disorder**	46	13	28	21	18	9
GDD**	44	13	28	21	16	8
ID	41	12	12	9	29	14
Genetic disorder	20	6	9	7	11	5
Cerebral palsy/PVL	18	5	11	8	7	3
Other	25	7	11	8	14	7
Reason for referral						
Aggression	188	54	67	49	121	58
Hyperactivity	101	29	43	32	58	28
Irritability	82	24	24	18	58	28
Anxiety	77	22	35	26	42	20
Self-injury	55	16	18	13	37	18
Inattention	47	14	24	18	23	11
OCD/OCD-like behaviors*	43	12	25	18	16	8
Sleep concerns	18	5	8	6	10	5
Emotional dysregulation/tantrums/meltdowns	17	5	3	2	14	7
Medication side effect	16	5	10	7	6	3
Oppositionality	11	3	5	4	6	3
Other	33	10	14	10	19	9
Referring provider						
Pediatrician	293	85	112	82	181	87
Psychiatrist	20	6	10	7	10	5
Family physician	17	5	5	4	12	6
Other	5	1	4	3	1	0
Not specified	10	3	5	4	5	2
Number of medications at time of clinic visit*						
None	67	19	35	26	32	15
One	140	41	55	40	85	41
Two	99	29	37	27	63	30
Three or more	39	11	9	7	29	14
Type of medication at time of clinic visit						
SGA*	151	44	48	35	103	49
Stimulant	73	21	22	16	51	24
SSRI	60	17	24	18	36	17
Clonidine/guanfacine	46	13	10	7	36	17
Melatonin	46	13	14	10	32	15
Benzodiazepine	33	10	15	11	18	9
Atomoxetine	11	3	5	4	6	3
Other	20	6	2	1	18	9

Children could have more than one diagnosis, reason for referral, and medication; percentages will not sum to 100%. ''Other'' diagnoses include fetal alcohol spectrum disorder, acquired brain injury, OCD, encephalitis/encephalopathy, and hydrocephalus (each with $n < 10$). ''Other'' reasons for referral include low mood, social skills deficit, learning difficulties, regression, sexual behaviors, and incontinence (each with $n < 10$). ''Other'' referring providers (each with total $n < 10$) included physiatrist, behavioral therapist, and psychologist. Types of medications included only psychoactive medications used for neurodevelopmental disorders, mental health conditions, or behaviors. ''Other'' medications (each with total $n < 10$) included first-generation antipsychotic, mood stabilizer, tricyclic antidepressant, beta-blocker, bupropion, trazodone, and morphine. Statistically significant differences between time periods: *$p < 0.05$; **$p < 0.01$.

ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; BMI, body mass index; CAMESA, Canadian Alliance for Monitoring of Effectiveness and Safety of Antipsychotics in Children; GDD, global developmental delay; ID, intellectual disability; OCD, obsessive compulsive disorder; SD, standard deviation; SGA, second-generation antipsychotic; SSRI, selective serotonin reuptake inhibitor.

Table 2. Second-Generation Antipsychotic Use and Monitoring Before Tertiary Clinic Consultation

	Pre-CAMESA (n = 48)	*Pre-CAMESA (%)*	*Post-CAMESA (n = 103)*	*Post-CAMESA (%)*
Duration of treatment				
Mean (SD)*	18.6 (14.7)		27.2 (24.6)	
Median	12		18	
Range	1–60		0.25–120	
Investigations completed before referral				
Any	17	35	39	38
All	7	15	26	25
Some	10	21	13	13
PRL	8	17	14	13
Cholesterol	12	25	20	18
AST/ALT	9	19	19	17
BG	10	21	17	16
Abnormal values	9	53	11	28
None	12	25	32	29
Missing	19	40	32	31

*$p < 0.05$.

ALT, alanine transaminase; AST, aspartate transaminase; BG, blood glucose; CAMESA, Canadian Alliance for Monitoring of Effectiveness and Safety of Antipsychotics in Children; PRL, prolactin; SD, standard deviation; SGA, second-generation antipsychotic.

additional finding of a longer duration of SGA treatment in this period, our results instead point to increased overall exposure to SGAs among these children.

In addition to the CAMESA guidelines, other antipsychotic monitoring recommendations have been published globally (Chokhawala and Stevens 2019). In 2003, the American Diabetes Association and American Psychiatric Association published guidelines that involve monitoring weight, BMI, lipid profile, and glucose. Many studies have since investigated the impact of these guidelines, and most have found minimal to no change in monitoring rates (Haupt et al. 2009; Morrato et al. 2010). Inconsistent clinical guideline uptake among health care practitioners is not a new health systems issue and several studies have proposed implementation frameworks to help close the gap between advancing research and improved patient outcomes. A scoping review by Fischer et al. (2016) proposed three factors that influence adherence to recommendations: personal factors, guideline-related factors, and external factors. Personal factors include physician knowledge and attitudes; guideline-related factors include applicability, accessibility, complexity, and evidence; external factors include organizational constraints and resource availability. In this case, patient-related factors may be important to consider in addition to other recognized factors. Despite clinicians' best efforts, difficulty obtaining blood work from patients with NDDs may pose a barrier to monitoring. Clinicians should make every reasonable effort to obtain blood work for SGA monitoring, including the use of toolkits (Autism Treatment Network 2011) and coordinating blood draws with procedures for which the child will be sedated (i.e., dental work). Quality improvement approaches may be helpful to implement and evaluate clinic processes that address relevant barriers and support routine monitoring.

Limitations of this study do exist. First, we used a convenience sample from a specialized tertiary psychopharmacology clinic in Toronto, Ontario. Comprehensive data collection was limited by the availability of information in patient charts. Laboratory monitoring was not consistently documented by the referring or the receiving provider. Results of laboratory monitoring were not always forwarded to the clinic, making it difficult to determine the true number of abnormal results. Although there was a high amount of ''missing'' data in this study, this finding in itself is important because documentation of laboratory testing informs ongoing management decisions. Thus, there may be a need for enhanced communication between community and tertiary providers so that all members of the circle of care are adequately informed of the risks and benefits of ongoing SGA treatment.

Conclusions

The proportion of children with NDDs who were prescribed an SGA increased between the pre- and post-CAMESA periods, as did the duration of exposure to SGAs. Concerningly, the proportion of children undergoing monitoring did not change after guideline publication. Future studies should determine how to effectively improve SGA monitoring.

Clinical Significance

This study evaluated whether pediatric antipsychotic guidelines changed monitoring rates in children with NDDs referred to a specialized psychopharmacology clinic. After guideline publication, there was no change in monitoring rates; however, more children were prescribed antipsychotics and children had been taking them for longer. More work is needed to identify barriers to antipsychotic monitoring in this population to balance risks and benefits of these medications.

Disclosures

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