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Metabolic monitoring in children 5 years of age and younger prescribed second-generation antipsychotic medications

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Abstract

Introduction: The objective of this article was to identify the rates of patients ≤5 years of age who received recommended monitoring before and after second-generation antipsychotic (SGA) initiation and had an SGA metabolic adverse effect (MAE).

Methods: This was a retrospective cohort analysis conducted at Kaiser Permanente Colorado, an integrated health care delivery system, between January 1, 2002, and June 30, 2011. Commercially insured patients ≤5 years of age newly initiated on an SGA were included. Patients were followed for up to 3 years. Metabolic monitoring included lipid profile, blood glucose, blood pressure, and weight measurements. Patient characteristics and outcomes were described using descriptive statistics.

Results: A total of 40 patients were included. Overall, 2 (5.0%) patients received all recommended baseline monitoring, and no (0.0%) patients received all recommended follow-up monitoring. Weight monitoring was completed most frequently with rates of completion of 57.5%, 95.0%, 85.0%, and 76.5% at baseline and years 1, 2, and 3, respectively. At least 1 MAE was identified in 14/40 (35.0%), 5/28 (17.9%), and 2/17 (11.8%) patients during years 1, 2, and 3, respectively. The most frequent MAE identified was weight gain. Among patients identified with at least 1 MAE, 4/14 (28.6%), 2/5 (40.0%), and 2/2 (100%) received a behavioral intervention during years 1, 2, and 3, respectively.

Discussion: Overall, baseline and follow-up metabolic monitoring were poor. Future studies should focus on examining barriers to monitoring in order to improve health care quality.

Keywords: antipsychotic agents, adverse effects, pediatrics, drug monitoring, integrated delivery of health care

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Introduction

The use of second-generation antipsychotics (SGA) in children ≤5 years of age is increasing despite limited FDA-approved indications.[1-3] State-specific research[2,4] in Medicaid populations has identified that antipsychotic use in children significantly increased over a 5-year period with rates of use in children ≤5 years of age ranging from 1.6% to 2.6%. Given the minimal benefit of SGA use in children, there are growing concerns about the risk of SGA-associated metabolic adverse effects (MAEs) and other associated abnormalities in this population.[2-9]

Studies[10-13] suggest that very young children may be the most susceptible to MAEs and endocrine abnormalities. Although monitoring can lead to early recognition of preventable SGA-induced MAEs, recommended monitor-

ing, based on the American Diabetes Association and American Psychiatric Association (ADA/APA) joint guidelines,[6] in children is not performed routinely.[3,14]

The effects of SGA use in children ≤5 years old, particularly within an integrated health care delivery system (IHCDS), are unclear. Because Medicaid beneficiaries experience poorer health outcomes compared with IHCDS patients, it is important to understand SGA use in non-Medicaid pediatric patient populations.[15] Thus, the purpose of this study was to evaluate SGA use, including rates of metabolic monitoring, MAEs, and management practices, in a population of children ≤5 years old.

Methods

Study Design and Setting

This was a retrospective cohort study of children ≤5 years of age who were newly initiated on an SGA (ie, clozapine, olanzapine, quetiapine, risperidone, ziprasidone, paliperidone, and aripiprazole). Patients were followed for up to 3 years after SGA initiation or until discontinuation of all SGAs or health plan membership termination, whichever came first. This study was conducted among members of Kaiser Permanente Colorado (KPCO), an IHCDS with more than 500 000 members receiving care at 25 ambulatory clinics at the time of the study. Patients were cared for through the integrated efforts of mental health providers, including child psychiatrists, nurses, clinical pharmacy specialists, and therapists.

Lipid and blood glucose laboratory results are processed at KPCO's laboratories. Kaiser Permanente Colorado utilizes an electronic medical record (EMR; Health Connect®, Epic Systems, Madison, WI) with which coded and free-text medical, pharmacy, laboratory, death, etc, information is recorded. Study information was obtained from queries of KPCO administrative databases and verified via manual EMR reviews. This study was reviewed and approved by the KPCO Institutional Review Board.

Study Population

Children were included if they had an SGA newly initiated between January 1, 2002, and June 30, 2011, and were ≤5 years of age at time of initiation. A SGA was considered newly initiated if there was no history of a SGA prescribed in the 180 days prior to the first dispensing (index date) during the study period. Included children had received ≥60-day supplies of the SGA during the 180-day period following the index date and maintained continuous KPCO membership during the 180 days prior to and after the index date.

Data Collection

The study cohort was identified through queries of KPCO's electronic administrative databases. Manual EMR reviews were conducted to identify behavioral interventions for MAEs and verify study outcomes as needed. Lipid and blood glucose values, blood pressure and weight measurements, patient mental health indication(s), and comorbidities (ie, hypertension, diabetes mellitus) were extracted from the EMR database. Prescription medication dispensing information in the 180 days prior to and after the index date were obtained from the electronic KPCO pharmacy database.

Study Outcomes

The primary study outcome was the percentage of patients who received all recommended metabolic monitoring, per the ADA/APA guidelines, at baseline and first-year follow-up after SGA initiation. The 1-year monitoring period allowed for the greatest capture of monitoring and is consistent with National Committee for Quality Assurance quality metrics for health plan performance.[16] Metabolic monitoring was defined as lipid profile (low-density lipoproteins and triglycerides), blood glucose, blood pressure, and weight measurements. Baseline monitoring was defined as having received a measurement during the 84 days prior to and up to 14 days after the index date. Follow-up monitoring was defined as having received a measurement during the first, second, and third years after the index date. Monitoring was assessed in patients who had at least one SGA dispensing and continued as a KPCO member during each follow-up year. For patients with a baseline monitoring in the 14 days after the index date, follow-up commenced on the day after the baseline monitoring date.

Secondary outcomes included an assessment of MAEs and any subsequent behavioral interventions for such effects. Behavioral interventions included diet and/or exercise counseling or referral to weight management for evaluation. An MAE was defined as weight ≥90th percentile, blood pressure >120/80 mmHg, triglycerides ≥110 mg/dL, or fasting blood glucose >100 mg/dL.[11,13,17] If a patient had more than 1 metabolic measurement in a study period, the measurement most proximal to but before the index date was used for the baseline value, and the measurement most distal to and after the index date but before the end of the study period was used for the follow-up value. Additional outcomes included SGA (eg, interchange to another SGA) and health services (eg, inpatient stays, emergency department visits) utilization. Further, subanalysis was performed to identify blood pressure >110/70 mmHg to account for potential hypertension in younger children.

Patient age was determined as of index date. Mental health indications were categorized as anxiety, autism, bipolar disorder, depression, mood disorder, hyperkinetic disorder, psychotic disorder, other, and unknown. Prescriber departments were categorized as mental health, other (eg, family practice, neurology, pediatrics), and hospital/non-KPCO provider. Race was categorized as white and other/unknown/unreported. Metabolic monitoring is reported as the percentage of patients who received specific monitoring by discrete study time periods. Behavioral interventions, MAEs, and health services utilization are reported as percentages.

Results

Forty patients were included and followed for a mean of 2.8 ± 0.8 years (Table 1). Patients were predominantly male, and the majority (57.5%) were 5 years of age. The majority of patients received risperidone as their index SGA with a median starting dose of 0.5 mg/d. The most common mental health indications were major depression and autism. Approximately half of prescribers were from the KPCO Mental Health Department. Although few patients had comorbidities, 5 patients were diagnosed with developmental delay.

Overall, 2 patients received all recommended baseline monitoring, and no patients received all recommended monitoring in any of the follow-up years (Table 2). The highest numerical rates of both baseline and follow-up monitoring were for weight and blood pressure. Baseline and follow-up rates of lipid and glucose were low. Twenty-eight (70.0%) and 17 (42.5%) patients had at least 1 SGA dispensing during years 2 and 3, respectively (Table 3). At least one MAE was identified in 14/40 patients during year 1, 5/28 patients during year 2, and 2/17 patients during year 3 (Table 3). The most frequent MAE identified was weight gain during years 1, 2, and 3. Among patients identified with a least 1 MAE, 4/14, 2/5, and 2/2 received a behavioral intervention during years 1, 2, and 3, respectively. Thirty-six of 40, 22/28, and 16/17 patients had at least 1 inpatient stay or emergency department visit, and 13/40, 9/28, and 6/17 patients had an interchange to another SGA during years 1, 2, and 3, respectively (Table 3).

TABLE 1: Patient characteristics

Characteristic	Value (N = 40)
Age at index SGA (n, %)	
3 years	4, 10.0%
4 years	13, 32.5%
5 years	23, 57.5%
Female (n, %)	6, 15.0%
Index SGA (n, %)	
Quetiapine	3, 7.5%
Risperidone	37, 92.5%
Index SGA median dose (mean, IQR)	
Quetiapine	50 mg (50 mg, 50–50 mg)
Risperidone	0.5 mg (0.6 mg, 0.3–0.5 mg)
Mental health indication[a] (n, %)	
ADHD	2, 5.0%
Autism	10, 25.0%
Bipolar disorder	2, 5.0%
Major depression	11, 27.5%
Psychotic disorder	1, 2.5%
Other[b]	12, 30.0%
Unknown	2, 5.0%
Other conditions[a] (n, %)	
Developmental delay	5, 12.5%
Diabetes mellitus	0, 0.0%
Dyslipidemia	0, 0.0%
History of child abuse	0, 0.0%
Hypertension	0, 0.0%
Obesity	0, 0.0%
Index SGA prescriber department (n, %)	
Mental health	18, 45.0%
Other	10, 25.0%
Prescribed in hospital/outside physician	12, 30.0%
Race (n, %)	
White	22, 55.0%
Other/unreported	18, 45.0%
Hispanic ethnicity (n, %)	6, 15.0%
Median family income at SGA initiation (IQR)	$64 633 ($51 458–$91 329)

ADHD = attention deficit hyperactivity disorder; IQR = interquartile range; SGA = second-generation antipsychotic.

[a]Recorded in a medical office visit in the 180 days prior to the index SGA purchase.

[b]"Other" includes ICD-9 diagnosis codes 300.xx, 307.xx, 308.xx, 309.xx, 310.xx, 311.xx, 312.xx, and 313.xx.

Discussion

Our retrospective cohort analysis of 40 IHCDS patients identified that children ≤5 years of age newly initiated on an SGA rarely received recommended baseline or follow-up metabolic monitoring. Although we found low rates of overall monitoring, weight and blood pressure monitoring were performed most often. The findings from our study are important as they add to the knowledge of SGA use in very young children who are not Medicaid beneficiaries.

The observed low rates of laboratory monitoring are similar to that reported in other settings. A study[9] of Medicaid-enrolled children who initiated an SGA identified

TABLE 2: Metabolic monitoring at baseline and by study year

Parameter	Baseline (N = 40)	Year 1 Follow-up (n = 40)	Year 2 Follow-up (n = 28)	Year 3 Follow-up (n = 17)
Received an SGA[a] (n, %)	40, 100.0%	40, 100%	28, 70.0%	17, 42.5%
Metabolic monitoring[b]				
Blood pressure (n, %)	18, 45.0%	36, 90%	23, 82.1%	13, 76.5%
Any blood glucose (n, %)	3, 7.5%	4, 10%	2, 7.1%	3, 17.8%
Any lipids (n, %)	5, 12.5%	4, 10%	1, 3.6%	2, 11.8%
Weight (n, %)	23, 57.5%	38, 95%	24, 85.7%	13, 76.5%
All monitorings[c] (n, %)	2, 5.0%	0, 0%	0, 0.0%	0, 0.0%

[a]Based on at least 1 outpatient dispensing of an SGA during the specific follow-up period.

[b]Among patients who had at least 1 outpatient dispensing of an SGA during the specific follow-up period; monitoring could be performed at any time during time period.

[c]Blood pressure, blood glucose, any lipid, and weight were all measured and recorded during the respective study periods.

TABLE 3: Medication and health services use, metabolic outcomes, and behavioral interventions by study year

Parameter	Year 1 Follow-up (n = 40)	Year 2 Follow-up (n = 28)	Year 3 Follow-up (n = 17)
Medication and health services use			
Mean SGA Days supply (SD)	300 (99)	242 (121)	264 (125)
Interchange to another SGA (n, %)	13, 32.5%	9, 32.1%	6, 35.3%
At least one inpatient stay/ED visit (n, %)	13, 32.5%	6, 21.4%	3, 17.7%
Mean count of inpatient stays/ED visits[a] (SD)	2 (1)	2 (1)	1 (1)
At least one outpatient mental health encounter (n, %)	36, 90.0%	22, 78.6%	16, 94.1%
Mean count of outpatient mental health encounters (SD)	13 (10)	9 (9)	11 (12)
Metabolic outcomes and behavioral interventions			
Any metabolic outcome (n, %)	14, 35.0%	5, 17.9%	2, 11.8%
Mean fasting glucose level[b] (SD)	89 (6)	84 (1)	86 (4)
Fasting glucose >100 mg/dL[b,c] (n, %)	0, 0.0%	0, 0.0%	0, 0.0%
Blood pressure >120/80 mmHg[b,d] (n, %)	0, 0.0%	0, 0.0%	0, 0.0%
Blood pressure >110/70 mmHg[b,e] (n, %)	0, 0.0%	0, 0.0%	0, 0.0%
Mean fasting triglycerides[b] (mg/dL, SD)	71 (40)	n/a	33 (14)
Fasting triglycerides >110 mg/dL[b,f] (n, %)	1, 33.3%	n/a	0, 0.0%
Mean pounds of weight change from baseline[g] (lbs, SD)	+13 (10)	+10 (9)	+18 (16)
Weight ≥90th percentile[h] (n, %)	13, 34.2%	5, 20.8%	2, 15.4%
Any behavioral intervention for metabolic outcome (n, %)	4, 28.6%	2, 40.0%	2, 100%
Behavioral intervention type (n, %)			
Exercise intervention	3, 75.0%	2, 100%	1, 50.0%
Diet intervention	4, 100%	2, 100%	2, 100%
Referral to intervention specialist	0, 0.0%	0, 0.0%	0, 0.0%

ED = emergency department; SGA = second generation antipsychotic.

[a]Among patients with at least 1 specific health services encounter.

[b]Among patients with a specific measurement.

[c]0/3 patients had a fasting glucose >100 mg/dL at baseline.

[d]0/18 patients had blood pressure >120/80 mmHg at baseline.

[e]1/18 patients had blood pressure >110/70 mmHg at baseline.

[f]0/4 patients had fasting triglycerides >110 mg/dL at baseline.

[g]Among patients with a specific measurement; change is from the previous time period.

[h]1/23 patients had weight ≥90th percentile at baseline.

that only 31% and 14% received glucose and lipid tests, respectively. Honey and colleagues[18] identified that 32 adolescent patients in a pediatric clinic received an SGA with only 13% receiving baseline monitoring.

Metabolic monitoring is a recognized challenge in young patients; collecting fasting laboratory samples can be difficult due to school schedules and parental work commitments.[18,19] In addition, patient and family understanding of SGA-associated risks and the need for monitoring may affect patient decisions to comply with laboratory monitoring. Parents may be reluctant to have monitoring performed that involves a needle-stick due to the potential for patient trauma, particularly in patients with autism. Consequently, there may be a similar hesitancy by prescribing providers to order laboratory monitoring. In a national survey[20] of child and adolescent psychiatrists, physicians were less likely to perform metabolic monitoring if they perceived a low metabolic risk with the SGA or expected poor adherence to laboratory monitoring.

In our study, 35% of patients experienced a MAE during year 1, followed by approximately 18% and 12% of patients in years 2 and 3, respectively. Most patients experienced weight gain, and 1 patient had elevated triglycerides. Although some of our patients were only prescribed an SGA for <1 year, MAEs, primarily weight gain, can occur within a short time frame after initiation,[7] and children and adolescents may be at greater risk for unhealthy weight gain with SGA use than adults.[21] This may be due to drug metabolism differences and lack of development in the prefrontal cortex, leading to dysregulation of the hypothalamus and, thus, increased caloric intake. Caution is warranted as weight gain and abnormal metabolic status in childhood are associated with poor cardiovascular outcomes in adulthood.[22,23]

In our study, we identified that a number of patients with an MAE received a behavioral intervention. Appropriate strategies to minimize metabolic complications include lifestyle interventions and reevaluation of SGA use if a mild MAE occurs. Discontinuing SGA, decreasing to the lowest dose, or interchange to another agent should be considered if a severe MAE occurs.[17] We identified that a large majority of the patients in our study had at least 1 mental health encounter during every year of follow-up. This finding is in contrast to Olfson and colleagues[6] who reported that only approximately 40% of the very young patients in their study had a mental health encounter. Conversely, we identified numerically larger proportions of patients with an inpatient stay/emergency department visit during follow-up than Olfson and colleagues[6] (≈25% versus ≈5%). This discrepancy is likely because Olfson and colleagues reported only mental health–related stays/visits and we reported all-cause stays/visits.

Implications for Providers

The expanded use of SGAs to younger children and the associated risk of adverse health outcomes have led to increased national attention. Quality measures pertaining to SGA use in young children have been developed. For example, the Pharmacy Quality Alliance's Antipsychotic Use in Children under Five Years Old addresses the percentage of children <5 years of age who receive an off-label prescription for an SGA.[1] This measure is designed to assess the number of children with ≥1 prescription for an SGA with a cumulative days' supply ≥30 days. Multiple stakeholders have commented that the increasing use of SGAs in children is concerning due to safety risks; thus, the implementation of quality measures may reduce gaps in care and ensure prudent SGA use.[16]

Although this study identified that recommended SGA metabolic monitoring in children ≤5 years of age is limited and MAEs were found in such patients who did have monitoring, many questions remain. For instance, what are the consequences of long-term SGA use that are not approved for or well-studied in this age group? Who should be responsible for ensuring monitoring—is this on the provider, parent, or insurer? Future studies should examine these critical questions.

Limitations

Although this study provides important information on SGA use in very young patients, it was limited by a lack of information surrounding family understanding of SGA risks and use of shared decision-making processes. Thus, we were unable to assess if a patient's family chose not to receive metabolic monitoring. In addition, we were unable to assess provider factors or other barriers to monitoring, including lab monitoring that had been ordered but not obtained. We also acknowledge that several changes occurred in practice standards and treatment options during the study time frame. For example, risperidone was approved for the treatment of irritability associated with autism in children 5 years and older in 2006, making it the first FDA-approved SGA available for use in children. Only 12.5% of our study patients were initiated on a SGA prior to this time. Furthermore, we had a small sample size; however, there is little information on SGA use published in this patient population, so our results may help to elucidate trends of SGA use and monitoring in pediatrics from an IHCDS. Last, although prescription refills could be assessed, we were unable to determine if patients actually ingested their prescribed medication.

Conclusions

Baseline and follow-up recommended metabolic monitoring was poor in an IHCDS population of children ≤5 years

of age who were newly initiated on an SGA. Among patients identified with an MAE, behavioral interventions were common. Future studies should focus on examining barriers to monitoring in order to improve health care quality.

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