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ORIGINAL RESEARCH

Relationships between the use of second-generation antipsychotics and changes in total cholesterol levels in children and adolescents perinatally infected with HIV

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Purpose: Perinatally HIV-infected children, who are increasingly aging into adolescence and early adulthood, have significant rates of psychiatric co-morbidities, some of which are treated with second-generation antipsychotics (SGAs). SGAs have been associated with elevated total cholesterol (TC) in youth, but no studies have examined this association in perinatally HIV-infected youth. This study examined changes in TC levels of youth with perinatally acquired HIV infection and co-morbid psychiatric conditions treated with SGAs.

Patients and methods: Long-term changes in TC levels were examined using data from the US multisite prospective Pediatric AIDS Clinical Trials Group 219C cohort study. The change in TC levels from baseline to 12 months after initiating SGA use was compared between 52 SGA-exposed and 148 matched SGA-unexposed perinatally HIV-infected youth, using generalized estimating equation models adjusting for other covariates. The prevalence and time to incident hypercholesterolemia were also compared between these 2 groups.

Results: After adjustment for confounders, 52 youth with prescriptions for SGAs had a larger increase in TC levels than 148 matched youth without antipsychotic prescriptions (mean difference = 9 mg/dL, z = 1.96, df = 1, $P = 0.0496$). Among youth with TC below 220 mg/dL at baseline, 27% of SGA-exposed youth developed hypercholesterolemia (defined as two consecutive TC measurements ≥220 mg/dL), compared with 13% of SGA-unexposed patients (Fisher's exact test, $P = 0.046$).

Conclusions: Caution should be used in prescribing SGAs to perinatally HIV-infected youth with psychiatric co-morbidities due to increased risk of hypercholesterolemia. Patients should be monitored, and alternative evidence-based treatments considered when available.

Keywords: HIV-infected youth with psychiatric co-morbidities, second-generation antipsychotics in youth, cholesterol in youth

Introduction

As the cohort of perinatally HIV-infected youth in the United States is aging into adolescence and early adulthood, the need for long-term management of highly prevalent co-morbid psychiatric symptoms in this unique population is growing.[1–5] As a result, physicians caring for these youth increasingly need to manage complex medication regimens that include not only highly active antiretroviral therapy (HAART), but also psychotropic medications, with limited safety data to use as guidance.

Second-generation antipsychotics (SGAs) are prescribed to treat a variety of psychiatric disorders in youth,[6–8] and most of them are approved by the US Food and Drug Administration for use in youth 13 years and older.[9–11] However, evidence suggests

that the use of SGAs might be associated with increased total cholesterol (TC) levels in youth.[12–14] Perinatally HIV-infected youth with psychiatric co-morbidities might be particularly vulnerable to this treatment complication and related health risks because: (1) they are more likely to receive psychotropic medications than their HIV-uninfected, sociodemographically matched peers;[15] (2) the prevalence of metabolic syndrome among HIV-infected individuals is growing;[16] and (3) treatment with protease inhibitors (PIs), a key component of most HAART regimens, has been associated with increased TC levels in perinatally HIV-infected youth.[17] On the other hand, evidence also suggests that psychopharmacologic safety data from the general population are not necessarily applicable to HIV-infected individuals; for example, prescribed stimulant medications did not show expected adverse impact on physical growth in a US cohort of perinatally HIV-infected youth,[18] and plasma concentrations of selective serotonin reuptake inhibitors (SSRIs) paroxetine and sertraline were found to be much lower in HIV-infected adults than in the general population, suggesting that HIV infection itself may alter pharmacokinetic profiles of these agents.[19] Thus, safety data specific for the distinct population of perinatally HIV-infected youth are needed to help prescribing clinicians optimize psychopharmacologic regimens and set parameters for monitoring treatment-emergent complications.

This study was designed to investigate the relationship between prescribed SGAs and changes in TC levels in a US cohort of perinatally HIV-infected youth. The hypothesis was that SGA treatment would be associated with increased TC levels.

Methods

Study design

This study evaluated data from the Pediatric AIDS Clinical Trials Group (PACTG), Protocol 219C (P219C), a multicenter, longitudinal observational cohort study of youth with HIV infection, acquired either perinatally or behaviorally, conducted from September 2000 until May 2007. P219C was a revision of PACTG Protocol 219, initiated in 1993 to study long-term effects of in-utero exposure to antiretroviral therapy (ART) and complications of HIV infection. Local institutional review boards, at over 80 participating sites in the US and Puerto Rico, approved P219C. Informed consent and assent were obtained per local institutional guidelines. Upon enrollment, study nurses abstracted participants' medical records to obtain medical and treatment histories, including diagnoses, ART, and concomitant medications. Follow-up visits included physical examinations, laboratory studies, and self-reports from children and primary caregivers (PCGs) to update demographic information, medical and treatment history, and quality-of-life information.

Participants

SGA exposure was defined as having a history of prescription for aripiprazole, clozapine, olanzapine, paliperidone, quetiapine, risperidone, or ziprazidone. The inclusion criteria for SGA -exposed youth from the P219C cohort were: perinatally HIV-infected, 3–22 years old at the time of SGA treatment, prescribed first SGA for at least 6 months, and had available baseline visit within 6 months prior to SGA initiation. Participants who were prescribed a conventional antipsychotic prior to SGA initiation were excluded. Each SGA-exposed participant was matched with up to 3 perinatally infected participants without SGA-exposure history. The matching was based on sex, birth date within 1 year, baseline Tanner stage category (Tanner 1–2, 3–4, or 5), and baseline TC within 15 mg/dL (roughly half of the standard deviation (SD) of TC measurements). The baseline visits for the SGA-exposed and matching unexposed participants were required to be within 3 months of each other.

Total cholesterol measurements

The TC measurements were scheduled to be conducted along with other routine laboratory studies at the time of each 3-month follow-up visit. Fasting was not required prior to these laboratory measurements. For SGA-exposed participants, the baseline TC measurement was the latest measurement prior to SGA initiation but no more than 6 months prior to SGA initiation. The follow-up TC measurement used for primary analysis was the measurement taken closest to 12 months after the baseline visit. This measurement was required to be obtained no less than 6 months after SGA initiation and within 18 months after the baseline visit, and to occur while the participant was still taking the first SGA. For the SGA-unexposed controls, the baseline measurement was the measurement taken closest to the baseline visit for the matching exposed participant. The follow-up measurement was the measurement taken closest to 12 months after the baseline visit and was between 6 and 18 months after the baseline visit.

Statistical methods

Primary analysis

The primary outcome was change in TC levels, as measured from a baseline visit to a follow-up visit (as described above). The primary analysis focused on comparison of change in TC

levels for perinatally HIV-infected youth with SGA exposure to those without antipsychotic exposure. A subgroup analysis compared participants with risperidone exposure with those without antipsychotic exposure.

Either Fisher's exact test or Pearson's chi-square test was used to compare patient characteristics between the SGA-exposed versus the unexposed group. A 2-sample *t*-test was used to compare length of follow-up time between the 2 groups. A 1-sample *t*-test was used to determine whether there was a significant average change in TC from baseline to follow-up in each group.

Univariate and multivariate generalized estimating equation models were used to evaluate the effect of SGA exposure and other variables on change in TC. Participant characteristics shown in Table 1 were considered as potential confounders in the model selection process. For the purpose of modeling, baseline values of the following variables were dichotomized: CD4 percent (>25% versus ≤25%), HIV RNA (>400 versus ≤400 copies/mL), CDC class (CDC class C versus other), PCG (biological parent versus other), and education level of PCG (high school graduate versus other). Race/ethnicity was collapsed into 3 categories (black non-Hispanic, Hispanic regardless of race, or white/other). ART use at baseline was considered as a categorical variable (HAART with PI, HAART without PI, ART without HAART, and no ART). HAART was defined as at least 3 drugs from at least 2 drug classes.

In selecting a multivariate model, all covariates with *P*-values <0.25 in either the univariate model or the full model, which contained all possible covariates, were considered to be candidates for inclusion. Covariates were removed using backward selection with a significance level of 0.10. ART use at baseline was included in the multivariate model regardless of significance because it has been identified as an important confounder in a similar study[17] and its effect was of particular interest. Duration of follow-up was also included in the final multivariate model regardless of significance.

Hypercholesterolemia analyses

To evaluate clinical relevance of the findings from the primary analysis, analyses of prevalence and time to incident hypercholesterolemia by SGA exposure were conducted. Prevalence was assessed at baseline and 6, 12, 18, 24, and 30 months from baseline. Incidence was assessed from baseline until the date the participant was last seen in the study. Because fasting was not required, the definition of incident hypercholesterolemia was modified to decrease false positives[17] as follows: the threshold TC value was raised from the usual 200 mg/dL to 220 mg/dL, and an incident case of hypercholesterolemia was defined as 2 consecutive values of 220 mg/dL or higher in a participant whose TC value was below 220 mg/dL at baseline. Incident hypercholesterolemia was assumed to occur at the time of the second TC measurement of 220 mg/dL and above. Fisher's exact test was used to compare incidence of hypercholesterolemia between the SGA-exposed and the unexposed group. Kaplan–Meier plots were constructed to estimate probabilities of hypercholesterolemia in each group.

Results

Of the 2589 perinatally HIV-infected youth in the P219C cohort, 119 (5%) had a history of receiving SGA prescriptions. Of these, 67 were excluded for the following reasons: incomplete drug history (n = 5), started SGA prior to study enrollment (n = 34), used first SGA for less than 6 months (n = 18), prescribed a conventional antipsychotic prior to or concurrently with an SGA (n = 1), discontinued the first SGA before a follow-up measurement was taken (n = 2), did not have either a baseline or a follow-up measurement within the specified time windows (n = 6), or did not have any matching controls available (n = 1). The remaining 52 SGA-exposed participants were included in the analysis. Matching up to 3 SGA-unexposed participants with each SGA-exposed participant resulted in 148 matched unexposed participants for a total sample size of 200. The risperidone subgroup analysis included 31 youth with risperidone prescriptions and 89 matched SGA-unexposed youth for a total sample size of 120.

Participant characteristics

Table 1 shows selected participant characteristics by SGA exposure, including demographic, disease, medication, and quality-of-life characteristics. Overall, the majority of participants were male (71%) and black non-Hispanic (54%). Most participants were in the 12–15 years age category (35%), followed by 9–12 (29%) and 6–9 years (21%). Compared with SGA non-exposed participants, the SGA-exposed cohort had a higher proportion of youth whose PCG was not their biological parent or relative ($\chi^2 = 10.6$, df = 4, $P = 0.03$), whose activities were limited by health (Fisher's exact test, $P = 0.02$), and who had at least one recorded neurologic or psychiatric diagnosis (documented as: "encephalopathy/cerebral palsy," "hypotonia," "microcephaly/failure to thrive," "epilepsy/seizure/infantile spasm," "ADHD/behavior disorder," "depression/anxiety/bipolar disorder," or "intellectual disabilities/developmental disorder") (Fisher's exact test, $P < 0.001$). There were no significant differences between the 2 cohorts with respect to race/ethnicity, CD4 percent,

Table 1 Participant characteristics

Characteristic		SGA exposure status			
		Not exposed	Exposed	Total	*P*-value
Age at baseline visit	3–6 years	8 (5%)	1 (2%)	9 (5%)	0.58[a]
	>6–9 years	31 (21%)	10 (19%)	41 (21%)	
	>9–12 years	41 (28%)	16 (31%)	57 (29%)	
	>12–15 years	51 (34%)	19 (37%)	70 (35%)	
	>15–18 years	8 (5%)	3 (6%)	11 (6%)	
	>18–22 years	9 (6%)	3 (6%)	12 (6%)	
Gender	Male	104 (70%)	37 (71%)	141 (71%)	1.00[b]
	Female	44 (30%)	15 (29%)	59 (30%)	
Tanner stage at baseline visit	1	82 (55%)	28 (54%)	110 (55%)	0.84[a]
	2	17 (11%)	8 (15%)	25 (13%)	
	3	14 (9%)	4 (8%)	18 (9%)	
	4	16 (11%)	2 (4%)	18 (9%)	
	5	19 (13%)	10 (19%)	29 (15%)	
Total cholesterol at baseline visit	170 or less	55 (37%)	19 (37%)	74 (37%)	0.76[a]
	>170–220	79 (53%)	30 (58%)	109 (55%)	
	>220	14 (9%)	3 (6%)	17 (9%)	
BMI at baseline visit	≤16	26 (18%)	9 (18%)	35 (18%)	0.99[a]
	<16–19	56 (39%)	19 (37%)	75 (38%)	
	19–22	32 (22%)	13 (25%)	45 (23%)	
	>22	31 (21%)	10 (20%)	41 (21%)	
Race/ethnicity	White non-Hispanic	19 (13%)	9 (17%)	28 (14%)	0.73[c]
	Black non-Hispanic	79 (53%)	29 (56%)	108 (54%)	
	Hispanic (regardless of race)	44 (30%)	14 (27%)	58 (29%)	
	Asian, Pacific Islander	2 (1%)	0 (0%)	2 (1%)	
	American Indian, Alaskan Native	2 (1%)	0 (0%)	2 (1%)	
	Subject does not know or other/unknown	2 (1%)	0 (0%)	2 (1%)	
CD4 percent	0–14	8 (6%)	3 (6%)	11 (6%)	0.87[a]
	15–25	31 (22%)	10 (20%)	41 (21%)	
	>25	104 (73%)	38 (75%)	142 (73%)	
HIV RNA (cp/mL)	0–400	75 (52%)	30 (58%)	105 (54%)	0.65[a]
	>400–10000	44 (31%)	13 (25%)	57 (29%)	
	>10000	25 (17%)	9 (17%)	34 (17%)	
CDC class	A	45 (30%)	19 (37%)	64 (32%)	0.49[a]
	B	58 (39%)	12 (23%)	70 (35%)	
	C	35 (24%)	14 (27%)	49 (25%)	
	N	10 (7%)	7 (13%)	17 (9%)	
ARV use at baseline	HAART with PI	104 (70%)	38 (73%)	142 (71%)	0.93[c]
	HAART without PI	16 (11%)	4 (8%)	20 (10%)	
	ART without HAART	19 (13%)	7 (13%)	26 (13%)	
	No ART	9 (6%)	3 (6%)	12 (6%)	
ARV regimen contains at least 1 PI at baseline	No	41 (28%)	13 (25%)	54 (27%)	0.86[b]
	Yes	107 (72%)	39 (75%)	146 (73%)	
PCG	Self (subject)	3 (2%)	2 (4%)	5 (3%)	0.03[c]
	Biological parent(s)	62 (42%)	17 (33%)	79 (40%)	
	Other relative	40 (27%)	7 (13%)	47 (24%)	
	Other adult	41 (28%)	23 (44%)	64 (32%)	
	Shelter/home	2 (1%)	3 (6%)	5 (3%)	
Education level, PCG	Other/unknown	14 (9%)	7 (13%)	21 (11%)	0.87[c]
	Grade 1–5/illiterate/none	35 (24%)	13 (25%)	48 (24%)	
	Grade 6–8	37 (25%)	14 (27%)	51 (26%)	
	Grade 9–11	40 (27%)	11 (21%)	51 (26%)	
	HS graduate	22 (15%)	7 (13%)	29 (15%)	
Had a recent stressful life event		62 (44%)	23 (45%)	85 (44%)	0.87[b]
Activities limited by health		8 (6%)	9 (19%)	17 (9%)	0.02[b]
Participated in school sports		96 (70%)	31 (63%)	127 (68%)	0.38[b]
At least one neurological diagnosis		47 (32%)	33 (63%)	80 (40%)	<0.001[b]

Notes: [a]Mantel-Haenszel chi-square; [b]Fisher's exact test; [c]Chi-square test.

Abbreviations: SGA, second-generation antipsychotic; BMI, body mass index; PCG, primary caregiver; HAART, highly active antiretroviral therapy; PI, protease inhibitors; ART, antiretroviral therapy.

HIV RNA (cp/mL), CDC disease severity class, ART use at baseline, recent stressful life events, participation in school sports, and education level of the PCG.

The most common first-prescribed SGA was risperidone, which was prescribed to 31 (60%) participants, followed by aripiprazole (n = 8; 15%), olanzapine (n = 7; 13%), quetiapine (n = 5; 10%) and ziprazidone (n = 1; 2%).

Table 2 shows the distribution of psychiatric and neurologic diagnoses among the participants included in the analysis. The most common documented diagnostic category overall was "ADHD/behavioral disorder" (n = 42; 21%), followed by "intellectual disabilities/developmental disorder" (n = 22; 11%) and "depression/anxiety/bipolar disorder" (n = 19; 10%). Among 52 SGA-exposed participants, 33 (63%) had at least 1 documented neurologic or psychiatric diagnosis. The SGA-exposed cohort had a significantly higher proportion of participants with a diagnosis of "ADHD/behavioral disorder" (Fisher's exact test, $P < 0.001$), "depression/anxiety/bipolar disorder" (Fisher's exact test, $P < 0.001$), and at least 1 documented neurologic or psychiatric diagnosis (Fisher's exact test, $P < 0.001$), as compared with the SGA-unexposed cohort.

Distributions of the baseline characteristics as well as psychiatric and neurologic diagnoses were similar among the risperidone-exposed participants (data available upon request).

Changes in total cholesterol (TC) levels

Mean and median TC increased in the SGA-exposed group, but decreased slightly in the unexposed group, resulting in a greater increase in TC in the SGA-exposed group (mean change = 10.4 mg/dL) than in the unexposed group (mean change = −0.8 mg/dL). 1-sample *t*-tests showed that the mean change in TC levels was significantly different from 0 in the SGA-exposed group (t = 2.32, df = 51, $P = 0.02$), but not in the SGA-unexposed group (t = −0.90, df = 147, $P = 0.37$). Variation in change in TC was higher in the exposed group (SD = 32.3) than in the unexposed group (SD = 10.4). This was due to some very large changes in TC values (outliers) observed in the exposed group. The distribution of follow-up times was comparable for the SGA-exposed and unexposed groups, with a mean length of follow-up of 11.9 months in the exposed group and 12.0 months in the unexposed group.

At baseline, mean TC and percentage of participants with elevated TC were comparable in the SGA-exposed and unexposed groups. During follow-up, mean TC and percentage with elevated TC were consistently higher in the SGA-exposed group (Figure 1).

Table 2 Frequencies of neurological and psychiatric diagnoses by SGA-exposure status

	Unexposed (N = 148)	Exposed (N = 52)	Total (N = 200)
Encephalopathy/ cerebral palsy	12 (8%)	6 (12%)	18 (9%)
Hypotonia	15 (10%)	3 (6%)	18 (9%)
Microcephaly/failure to thrive	8 (5%)	1 (2%)	9 (5%)
Epilepsy/seizure/ infantile spasm	5 (3%)	4 (8%)	9 (5%)
ADHD/behavior disorder	17 (11%)	25 (48%)	42 (21%)
Depression/anxiety/ bipolar disorder	6 (4%)	13 (25%)	19 (10%)
Intellectual disabilities/ developmental disorder	16 (11%)	6 (12%)	22 (11%)
At least one of the above	47 (32%)	33 (63%)	80 (40%)
None of the above	101 (68%)	19 (37%)	120 (60%)

Abbreviations: SGA, second-generation antipsychotic; ADHD, attention deficit/hyperactivity disorder.

Relationships between SGA exposure and TC changes

Table 3 summarizes the results of the univariate and multivariate models for TC on SGA exposure. Unadjusted for potential confounders, SGA-exposed participants experienced an average increase in TC during follow-up that was approximately 11 mg/dL higher than those in the unexposed group (z = 2.45, df = 1, $P = 0.01$). ART use at baseline was predictive of change in TC levels ($\chi^2 = 8.56$, df = 3, $P = 0.04$). Both HAART without PI (z = −1.89, df = 1, $P = 0.06$) and no ART (z = −2.55, df = 1, $P = 0.01$) were associated with smaller increases in TC than HAART with PI. There was no significant difference in change in TC between the ART without HAART group and the HAART with PI group.

The effect of SGA exposure remained significant in the multivariate model. After adjustment for confounders, SGA-exposed participants had an average increase in TC during follow-up that was approximately 9 mg/dL higher than in the SGA-unexposed participants (z = 1.96, df = 1, $P = 0.0496$). ART use was not significant in the multivariate model.

Unadjusted for potential confounders, risperidone-exposed participants experienced an average change in TC during follow-up that was approximately 14 mg/dL higher than in the unexposed participants (z = 2.08, df = 1, $P = 0.04$). ART use at baseline was not significantly associated with TC levels. The effect of risperidone exposure was marginally significant in the multivariate model. After adjustment for confounders, patients exposed to risperidone had an average increase in TC during

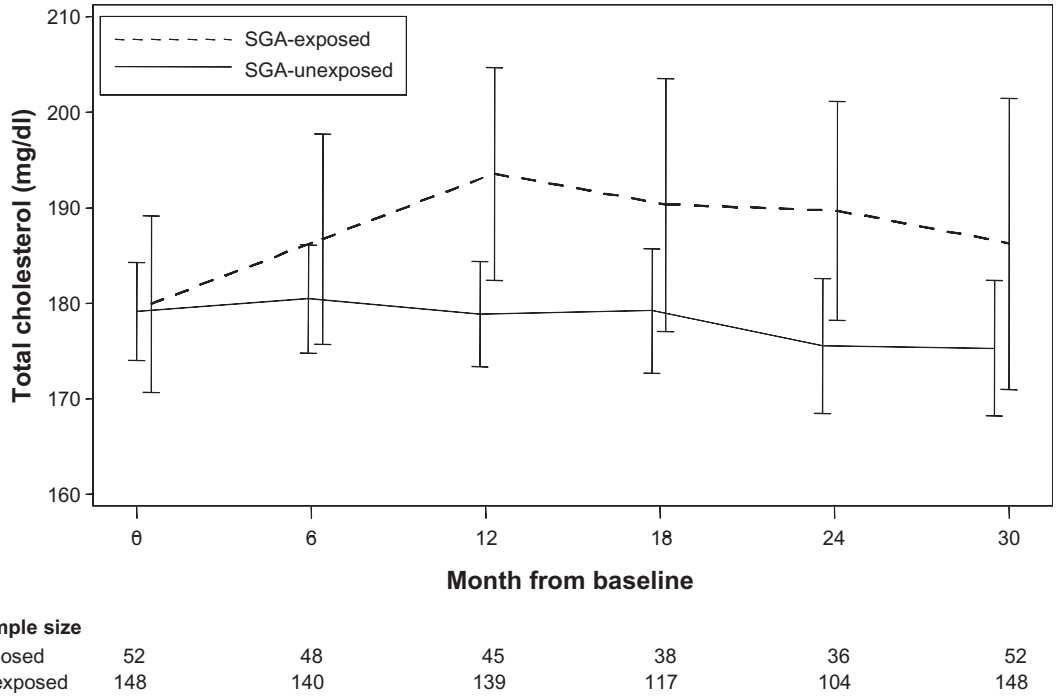

Figure 1 Mean total cholesterol over time, by SGA exposure, with 95% confidence intervals. The mean TC at a given time point included measurements that occurred within 3 months of that time point. If a participant had more than 1 measurement in this window, then the measurement closest to the time point was used.
Abbreviations: SGA, second-generation antipsychotic; TC, total cholesterol.

follow-up that was approximately 13 mg/dL higher than in the unexposed patients (z = 1.92, df = 1, $P = 0.055$).

Hypercholesterolemia analyses

Prevalence of hypercholesterolemia

The percentage of participants with elevated TC at baseline (defined as 220 mg/dL or higher) was comparable in the SGA-exposed and unexposed groups (6% versus 9%, Fisher's exact test, $P = 0.57$) (Figure 1).

Incidence of hypercholesterolemia

Of the 183 participants with TC below 220 mg/dL at baseline, 31 (17%) developed hypercholesterolemia during a median follow-up time of 28.9 months. Of the 134 unexposed participants with TC below 220 mg/dL at baseline, 18 (13%) developed hypercholesterolemia, compared with the 49 SGA-exposed patients with TC below 220 mg/dL at baseline, of whom 13 (27%) developed hypercholesterolemia (Fisher's exact test, $P = 0.046$). Figure 2 shows the Kaplan–Meier survival curves for the probability of staying hypercholesterolemia-free by exposure status; SGA-exposed participants had a lower probability of remaining hypercholesterolemia-free compared with unexposed participants. Among SGA-exposed participants who developed hypercholesterolemia, the median time to hypercholesterolemia was 16.8 months.

Discussion

This study examined relationships between prescribed SGAs and changes in TC levels in a cohort of perinatally

Table 3 Summary of estimated increase in total cholesterol over approximately 12 months for SGA (or risperidone)-exposed versus SGA (or risperidone)-unexposed youth

Model	SGA exposure			Risperidone exposure		
	Estimate (mg/dL)	95% confidence interval	*P*-value	Estimate (mg/dL)	95% confidence interval	*P*-value
Unadjusted	11.12	(2.21, 20.02)	0.01	13.56	(0.77, 26.35)	0.04
Multivariate model[a]	8.68	(0.01, 17.34)	0.0496	13.02	(–0.25, 26.30)	0.055

Notes: [a]Adjusted for statistically significant covariates (race/ethnicity, primary caregiver, education level of the primary caregiver, limited activity due to health) and covariates chosen a priori as important confounders (4-category ARV use and length of follow-up).
Abbreviation: SGA, second-generation antipsychotic.

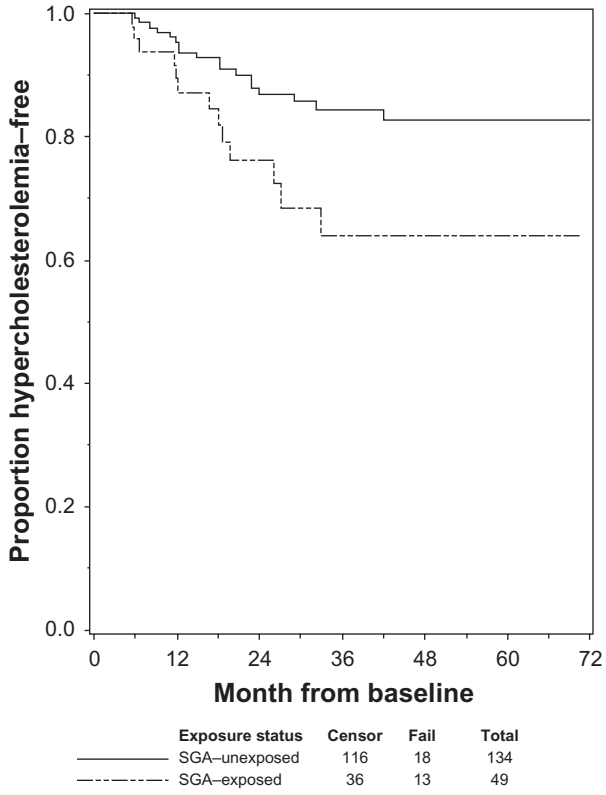

Figure 2 Estimated probability of remaining free of hypercholesterolemia, by SGA-exposure.
Abbreviation: SGA, second-generation antipsychotic.

HIV-infected youth. Exposure to SGAs as a class, as well as to risperidone alone, was associated with significantly increased TC levels over an average period of approximately 12 months. While the absolute values of the observed increases may not seem particularly high (9 mg/dL for SGA class and 13 mg/dL for risperidone alone), the statistical significance of these results, combined with matching of participants' sex, age, baseline Tanner stage category, and baseline TC, suggests that the increases are attributable to the SGA exposure alone. Furthermore, the incident analyses showed that SGA exposure was predictive of incident hypercholesterolemia, supporting the clinical significance of the TC increase.

Our data do not provide sufficient information to speculate about possible mechanisms of the observed associations. Findings from *in vitro* studies[20] and model analyses[21] suggest that SGA's affinity for histamine H1- and serotonin 5-HT2C receptors might affect hypothalamic control of appetite regulation and energy expenditure.[20–22] Alternatively, *in vitro* data suggest that certain SGAs might induce stimulation of cellular lipogenesis, thus raising the risk of dyslipidemia.[23] Similar mechanisms might be involved in SGA-associated increases in cholesterol in perinatally HIV-infected youth with psychiatric co-morbidities. Yet, in the latter group, these mechanisms might be further aggravated by the mechanisms of HAART-associated hypercholesterolemia that has been demonstrated in pediatric observational studies.[17,24]

Clinically, these findings should be viewed in the context of the already complex medical status of perinatally HIV-infected youth with psychiatric co-morbidities, including the growing rates of metabolic syndrome among HIV-infected adults.[16] Cholesterol levels should be routinely monitored when SGAs are being prescribed to youth with perinatally acquired HIV infection. Close communication should be maintained between the consulting psychiatrists, pediatricians and/or infectious disease specialists involved in the child's care and nutritional counseling provided. The youth and their caregivers should be educated about the potential for SGA-related TC increase, as well as other complications previously reported in perinatally HIV-infected youth treated with SGAs, such as increased body mass index *z*-scores.[25] Careful risk-benefit analysis should always be included in this process, given the known benefits of SGAs in treatment of certain psychiatric disorders in youth,[8] and potential impact of untreated psychotic symptoms on their medical care, safety, and overall quality of life.

This study has several limitations. First, SGA treatment was not randomly assigned. Some participant characteristics that were in existence prior to SGA initiation, and were not included in the matching criteria, could have influenced the cholesterol outcomes. Randomization would have minimized such potential confounding effects. Next, because P219C did not include complete lipid profiles, the study outcome was reduced to TC alone. Not requiring fasting prior to TC measurement was another limitation, which we attempted to minimize by raising the threshold TC value well above 200 mg/dL and requiring this higher threshold to have been met at 2 consecutive study visits for defining hypercholesterolemia. However, as discussed at length in a related publication,[7] elevated TC alone has been independently associated with a risk for early atherosclerotic disease,[26] and non-fasting TC is considered a useful screening tool for pediatric dyslipidemia.[27]

In conclusion, the present study demonstrated a significant potential of SGAs to contribute to increased TC levels in perinatally HIV-infected youth with psychiatric co-morbidities. The issue has high clinical relevance against the backdrop of dramatically increased lifespan and high rates of psychiatric co-morbidities in this population, as well as growing trends of prescribing SGAs to youth with various psychiatric conditions. When considering prescribing an SGA, clinicians should exercise caution and consider other evidence-based treatments where appropriate.

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