ARTICLE

Controller Medication Use and Sleep Problems in Pediatric Asthma

A Longitudinal Case-Crossover Analysis

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Objective: To determine the effect of asthma controller medication use, choice, and adherence on sleep in children with asthma.

Design: A case-crossover analysis examining within-subject differences in controller use between time points with and without sleep problems, based on survey data from 3 time points (baseline, 6 months, and 1 year) of a randomized trial.

Setting: Families were recruited from 2 area practice networks; all assessments were completed by parents online.

Participants: Children with asthma, aged 2 to 10 years, as identified by asthma-related medical encounters and prescription fills.

Main Exposures: Parent report of asthma controller medication use (yes/no), type (inhaled corticosteroid or leukotriene inhibitor), and adherence (daily use, nonadherent use, or nonuse).

Main Outcome Measures: Children's sleep problems, as defined by parent report regarding how often the child had difficulty falling asleep or experienced daytime sleepiness.

Results: The analysis included 482 children; 82.6% and 75.9% completed the 6-month and 1-year follow-up visits, respectively. Sleep problems were common, with 19.4% of parents at baseline reporting frequent problems with the child falling asleep and 12.1% reporting frequent daytime sleepiness. Compared with children who did not use a controller medication, children had a decreased risk of problems falling asleep during periods with daily controller use (odds ratio [OR], 0.34; 95% confidence interval [CI], 0.13-0.92), with a trend toward an effect in those with nonadherent use (0.47; 0.20-1.12). Any controller use, regardless of adherence, was also associated with decreased odds of daytime sleepiness (OR, 0.69; 95% CI, 0.51-0.94). When controller class was examined, leukotriene inhibitors were associated with significantly decreased odds of problems falling asleep (OR, 0.18; 95% CI, 0.04-0.78), with or without concomitant use of inhaled corticosteroids, but the results for use of inhaled corticosteroids alone were not statistically significant (0.69; 0.32-1.53).

Conclusions: Controller medications appear to be effective in reducing sleep problems in children with asthma, and leukotriene inhibitor medications may be especially effective in this population.

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CHILDREN WITH ASTHMA ARE at increased risk for a variety of sleep problems, including delayed sleep onset, increased night awakenings, and daytime tiredness.[1-4] This negative effect on sleep is observed even in children and young adults whose daytime asthma symptoms are well controlled[1,5,6]; however, children with poorly controlled asthma report more sleep problems than children with well-controlled asthma.[7] There is a variety of pathways involved, including both nighttime asthma symptoms and the increased prevalence of anxiety[4] and obstructive sleep apnea (OSA)[8,9] in children with asthma. Sleep problems, in turn, increase children's risk for a variety of negative outcomes, including behavior and emotional problems,[10-13] poor academic performance,[13-16] and excessive weight gain.[17,18] Furthermore, some research[19] has suggested that poor sleep in children may itself exacerbate asthma symptoms.

Compared with placebo, controller use in children with asthma has been shown to improve sleep. In a randomized, double-blind trial,[20] use of inhaled fluticasone propionate was associated with a significant decrease in sleep problem scores at 24 and 52 weeks into treatment. The comparative effects of different currently recommended controller medications on children's sleep are unknown; previous studies[21,22] have focused mostly on medications no longer recommended as pri-

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mary controller medications in children. However, one study[23] comparing the effects of different medications for perennial rhinitis found that leukotriene inhibitors improved children's sleep compared with cetirizine. Furthermore, although daily adherence to controller medications has been shown to improve asthma symptoms in both children and adults,[24] it is not known whether the same relationship would be observed when examining sleep problems.

In the context of an ongoing randomized controlled trial, we examined the impact of controller medication use, adherence, and controller choice on sleep problems in children, using a case-crossover model, because this has the advantage of eliminating much of the bias associated with unmeasured confounding factors.[25-30] In a case-crossover model, exposures (in this case, controller medication use) are compared during periods with and without the outcome of interest (sleep problems) within the same individual.

METHODS

We conducted a case-crossover analysis on a longitudinal sample of children; both predictors and outcomes were measured at 3 time points (baseline, 6 months, and 1 year), allowing us to examine within-subject differences in controller medication use between time points with and without parent-reported sleep problems. The University of Washington Institutional Review Board approved this study protocol.

STUDY SAMPLE

The study sample included children aged 2 to 10 years with asthma whose parents were enrolled in a clinical trial of an Internet-based asthma education intervention. As such, there was no experimental assignment of medication use; all clinical asthma care and prescriptions were provided by the child's usual provider. Families were recruited from 2 area practice networks; those with an age-eligible child with asthma were sent a letter informing them of the study and then contacted via telephone for recruitment. Enrolled parents completed an informed consent form and a baseline survey online covering their child's asthma symptoms, quality of life, sleep, demographic characteristics, and parent attitudes and beliefs. For the next 5 months, they were sent monthly e-mail reminders to log on to the Web site and complete a monthly session and survey; follow-up e-mails were sent at 1 and 2 weeks to parents who either did not log on or did not complete a session, and staff contacted, by telephone, those who did not log on after receiving 3 e-mails.

For families in the intervention group, these Web sessions assessed asthma symptoms and medication use, provided parents with feedback, identified potential areas for health behavior change for asthma care, led parents through goal-setting and problem-solving, and generated a report that parents were encouraged to share with the child's health care providers. Targeted goals were based on the National Heart, Lung, and Blood Institute asthma guidelines[31] and included the initiation of controller medications, improved adherence to controller medications, and having an up-to-date, written asthma care plan. Families in the control group received a sham intervention about healthy media use, designed to require the same amount of time each month to complete. At months 6 and 12, families from both study arms were sent e-mails asking them to complete a follow-up survey online, again assessing asthma symptoms and medication use, quality of life, and their child's sleep.

Among the 603 families initially enrolled in the study, 515 (85.4%) completed the 6-month follow-up and 480 (79.6%) completed the 12-month follow-up. The analyses reported herein were restricted to children for whom controller medications were indicated according to National Asthma Education and Prevention Program guidelines[31] (ie, those meeting criteria for persistent asthma based on parent report regarding frequency of daytime and nighttime asthma symptoms and bronchodilator use or those already receiving controller medications) at any measurement time point during the study period (N=482). According to the National Asthma Education and Prevention Program guidelines, children were classified as having persistent asthma (vs mild, intermittent asthma) for a given time point if parents reported daytime symptoms 3 or more days each week, nighttime symptoms more than twice monthly, or use of quick-relief medication 3 or more days each week. Within the persistent asthma group, children were categorized at each time point as having mild, moderate, or severe persistent asthma based on symptom frequency.

OUTCOMES

Sleep was assessed as part of asthma-related quality of life, and analytic outcomes were whether the child frequently (4-7 days a week) had difficulty falling asleep or experienced daytime sleepiness according to parent report at each time point. The questions were phrased as "had a hard time falling asleep at night" and "seemed sleepy or tired during the day," with response options of "not at all," "1 day a week,""2 or 3 days a week," "4 to 5 days a week," and "6 to 7 days a week."

PREDICTORS

In the adherence analyses, parent-reported controller use "during a recent typical week" was categorized at each time point as no use, nonadherent use (1-6 days a week), or daily use (7 days a week). For children using more than 1 controller medication, adherence was categorized according to the controller medication used most often.

In the analyses examining controller choice, inhaled corticosteroids and leukotriene inhibitors were examined, with the predictor classified during each period as (1) nonuse as the reference category, (2) inhaled corticosteroid use without leukotriene inhibitor use, (3) use of an inhaled corticosteroid and leukotriene inhibitor, or (4) leukotriene inhibitor use without an inhaled corticosteroid. Other controller medications (eg, long-acting bronchodilators, cromolyn sodium, and theophylline) were not used by enough children to be included as separate categories in these analyses. Wald tests were used to compare regression coefficients across controller categories, and categories were combined if $P > .50$ for the difference between coefficients.

ANALYSIS

All analyses used logistic regression models conditioned on the child's study identification number and were conducted using statistical software (Stata/SE 10; StataCorp LP, College Station, Texas). Children were thus compared only with themselves and so may, for example, have had controller medication use from 1 period with sleep problems compared with 2 periods without sleep problems. Because sleep problems tend to improve in children this age, all regression models included a term for the measurement time point.

The intervention aimed to improve controller use and adherence, and neither the intervention group nor the control group received any information about child sleep. Furthermore, the impact of any given level of controller use or adher-

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Table 1. Study Population at Baseline, 6 Months, and 1 Year

Demographics	Percentage		
	Baseline (N=482)	6-mo Follow-up (n=398)	1-y Follow-up (n=366)
Female sex	33.5		
Child age, y			
2-4	30.7		
5-7	30.7		
8-10	38.6		
Mean (SD)	6.2 (2.6)		
Race and ethnicity[a]			
White	75.9		
Asian	11.4		
Black	14.7		
Hispanic	7.3		
Pacific Islander	0.6		
Native American	2.5		
Other	6.0		
Multiracial	16.8		
Parent education			
≤High school	10.9		
Community or technical college	14.3		
Some college	25.4		
Bachelor's degree	25.4		
Graduate degree or professional	24.1		
Asthma severity			
Mild intermittent	63.5	75.1	74.3
Mild persistent	25.7	16.6	17.2
Moderate persistent	7.9	5.3	5.2
Severe persistent	2.9	3.0	3.3
Controller medication use			
None	31.7	31.7	35.8
Nonadherent	32.4	29.2	27.3
Daily	35.9	39.2	36.9
Controller medication			
Any	68.3	68.4	64.2
Inhaled corticosteroid	62.0	63.6	59.9
Leukotriene inhibitor	16.0	12.3	12.8
Long-acting bronchodilator	5.4	5.5	4.4
Systemic corticosteroid	6.6	5.5	5.2
Sleep			
Problems falling asleep 4-7 nights/wk	19.3	17.1	13.6
Daytime sleepiness 4-7 d/wk	12.1	9.7	7.2

[a] Categories are not mutually exclusive.

ence on child sleep outcomes is expected to be the same, regardless of study arm assignment. To test this assertion, we examined each model for potential effect modification by study arm assignment from the randomized trial (intervention vs control). We also tested for effect modification by child age (2-5 years vs 6-10 years).

RESULTS

The study sample for these analyses included 482 children who met National Heart, Lung, and Blood Institute criteria for controller medication use at some point during the study; 82.6% and 75.9% completed the 6-month and 1-year follow-up visits, respectively. At baseline, the eligible sample was 33.5% female and had a mean age of 6.2 years (**Table 1**). Overall asthma severity was relatively low, with 89.2% of the sample being classified

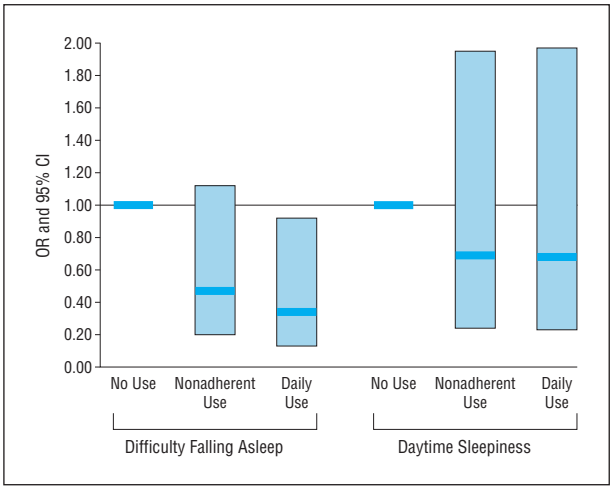

Figure. The effect of controller use and adherence on sleep problems. CI indicates confidence interval; OR, odds ratio. The horizontal line represents the reference OR; the group with no use is the reference group.

at baseline as mild intermittent or mild persistent. Consistent with guideline recommendations for this age group, inhaled corticosteroids were used more commonly than any other controller medication class. Among children using leukotriene inhibitor medications, 64.9% were also using inhaled corticosteroids. Sleep problems were common, with 19.3% of parents at baseline reporting frequent problems with the child falling asleep, and 12.1% reporting frequent daytime sleepiness.

The adherence analysis (**Figure**) showed a decreased risk of problems falling asleep during periods with daily controller use (odds ratio [OR],0.34; 95% confidence interval [CI], 0.13-0.92), with a trend toward an effect in periods with nonadherent use (0.47; 0.20-1.12) compared with periods of nonuse as a reference category. The effects of controller use and adherence on daytime sleepiness were not statistically significant; however, after the categories of daily use and nonadherent use were combined, we noted significantly reduced odds of daytime sleepiness during periods with any controller use (OR,0.69; 95% CI, 0.51-0.94).

In the analyses comparing periods with different controller medication choices, no significant effect was observed for inhaled corticosteroid use without leukotriene inhibitors (**Table 2**). Within children, similar results for difficulty falling asleep were seen between periods with leukotriene inhibitor use with (OR,0.19; 95% CI, 0.04-1.02) and without (0.17; 0.03-1.11) concomitant inhaled corticosteroids, and so the 2 categories were collapsed for the final models. We then noted significantly decreased odds of difficulty falling asleep during periods of leukotriene inhibitor use with or without inhaled corticosteroids (OR,0.18; 95% CI, 0.04-0.78), but no significant effect for inhaled corticosteroids (0.69; 0.32-1.53). Leukotriene inhibitor categories were likewise collapsed in the final model of daytime sleepiness, in which we observed a trend toward an effect (OR,0.20; 95% CI, 0.03-1.21). Again, the findings for inhaled corticosteroid use alone were not significant (OR,0.94; 95% CI, 0.34-2.58). There was no significant effect modification by study arm or age group for any of the models.

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Table 2. Controller Medication Choices and Effect on Sleep Problems

Controller Medication	Difficulty Falling Asleep		Daytime Sleepiness	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
None	1 [Reference]		1 [Reference]	
Inhaled corticosteroid	0.69 (0.31-1.53)	.36	0.89 (0.32-2.46)	.82
Inhaled corticosteroid + leukotriene inhibitor	0.19 (0.04-1.02)	.05	0.26 (0.04-1.79)	.17
Leukotriene inhibitor	0.17 (0.03-1.11)	.06	0.00 (null)	.99
None[a]	1 [Reference]		1 [Reference]	
Inhaled corticosteroid[a]	0.69 (0.32-1.53)	.36	0.94 (0.34-2.58)	.90
Leukotriene inhibitor ± inhaled corticosteroid[a]	0.18 (0.04-0.78)	.02	0.20 (0.03-1.21)	.08

Abbreviations: CI, confidence interval; OR, odds ratio; +, with; ±, with or without.
[a]Collapsed model.

COMMENT

Daily adherence to controller medications is associated with a significant reduction in parent perception of problems falling asleep among children with asthma. In addition to the clinical significance of improved sleep, the potential reduction in sleep onset problems may be a "selling point" for providers trying to increase parental motivation to initiate controller use or increase adherence. Not surprisingly, a previous study[20] that found a benefit of controller use on sleep problems in children with asthma also showed a significant effect on the parents' quality of life.

Another interesting finding in our study was that a significant effect on difficulty falling asleep was observed with leukotriene inhibitors but not with inhaled corticosteroid medications. One possible explanation for this finding lies in the high frequency of comorbid OSA and allergic rhinitis in children with asthma. Both OSA and allergic rhinitis are also associated with sleep problems in children, and systemic medications such as leukotriene inhibitors may be more likely to ameliorate associated upper airway inflammation compared with controller medications that are inhaled by mouth. Furthermore, leukotriene pathways have been implicated in the pathologic factors of pediatric OSA,[32-34] and at least one study[35] has observed improvement in sleep and biomarkers after the use of leukotriene inhibitors in children with mild OSA. Unfortunately, data were not collected in the present study on the concomitant use of intranasal corticosteroids, which are associated with improved child sleep in the context of both allergic rhinitis and mild OSA. Further study is needed to confirm the potential independent benefit of leukotriene inhibitors for sleep problems in children with asthma and to explore the degree to which this benefit may depend on the presence of comorbid upper airway conditions.

There are additional limitations of this study. Most notable is that both child sleep problems and asthma medication use were assessed by retrospective parental report and so may be subject to recall bias. However, because the case-crossover analyses compared outcomes within the same child and degree of recall bias is likely to remain relatively stable with the same parent, such misclassification would tend to bias the findings toward the null hypothesis. In addition, we had neither the data nor the sample size to examine potential effect modifiers of the relationships observed, such as exposure to secondhand smoke or seasonal allergies.

Despite these limitations, there are significant implications to our findings. Sleep problems in children with asthma are common and worth mitigating given their independent association with other morbidities. Future asthma research should include prospective assessment of children's sleep using validated measures, especially in randomized trials comparing different classes of controller medications. In the interim, our results suggest that leukotriene inhibitor therapy may proffer distinct benefits for children with asthma and concurrent sleep problems, especially among those whose sleep problems have not improved during treatment with other controller medications.

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