

Most nocturnal asthma symptoms occur outside of exacerbations and associate with morbidity

Caroline C. Horner, MD,^a David Mauger, PhD,^b Robert C. Strunk, MD,^a Nora J. Graber, MS,^b Robert F. Lemanske, Jr, MD,^c Christine A. Sorkness, PharmD,^d Stanley J. Szeffler, MD,^e Robert S. Zeiger, MD, PhD,^{f,g} Lynn M. Taussig, MD,^h and Leonard B. Bacharier, MD,^a for the Childhood Asthma Research and Education Network of the National Heart, Lung, and Blood Institute* *St Louis, Mo, Hershey, Pa, Madison, Wis, Denver, Colo, and San Diego, Calif*

Background: Although nocturnal awakenings help categorize asthma severity and control, their clinical significance has not been thoroughly studied.

Objective: We sought to determine the clinical consequences of nocturnal asthma symptoms requiring albuterol (NASRAs) in children with mild-to-moderate persistent asthma outside of periods when oral corticosteroids were used for worsening asthma symptoms.

Methods: Two hundred eighty-five children aged 6 to 14 years with mild-to-moderate persistent asthma were randomized to receive one of 3 controller regimens and completed daily symptom diaries for 48 weeks. Diary responses were analyzed for the frequency and consequences of NASRAs.

Results: NASRAs occurred in 72.2% of participants at least once, and in 24.3% of participants, they occurred 13 or more times. The majority (81.3%) of nocturnal symptoms occurred outside of exacerbation periods and were associated the next day with the following events: albuterol use (56.9% of days preceded by nocturnal symptoms vs 18.1% of days not preceded by nocturnal symptoms; relative risk [RR], 2.3; 95% CI, 2.2-2.4), school absence (5.0% vs 0.3%; RR, 10.6; 95% CI, 7.8-14.4), and doctor contact (3.7% vs 0.2%; RR, 8.8; 95% CI, 6.1-12.5).

Similar findings were noted during exacerbation periods (RRs of 1.7 for albuterol use, 5.5 for school absence, and 4.9 for doctor contacts). Nocturnal symptoms did not predict the onset of exacerbations.

Conclusion: Nocturnal symptoms requiring albuterol in children with mild-to-moderate persistent asthma receiving controller therapy occurred predominantly outside of exacerbation periods. Despite being poor predictors of exacerbations, they were associated with increases in albuterol use, school absences, and doctor contacts the day after nocturnal symptom occurrences. (*J Allergy Clin Immunol* 2011;■■■:■■■-■■■.)

Key words: Asthma, nocturnal symptoms, exacerbation

The frequency of nocturnal awakenings is used to categorize asthma severity and control based on expert-opinion consensus.¹ Although these nocturnal events are considered important in childhood asthma, their significance remains unclear because of a paucity of literature regarding this topic, in part because of the fact that most publications investigating nocturnal asthma have focused on adults.²⁻⁵ Studies in children have examined

From ^athe Department of Pediatrics, Washington University School of Medicine and St Louis Children's Hospital; ^bthe Department of Public Health Sciences, Pennsylvania State University, Hershey; ^cthe Department of Pediatrics and ^dthe School of Pharmacy and the Department of Medicine, University of Wisconsin School of Medicine and Public Health, Madison; ^ethe Department of Pediatrics, National Jewish Health, Denver; ^fthe Department of Pediatrics, University of California-San Diego; ^gthe Department of Allergy, Kaiser Permanente Southern California, San Diego; and ^hthe Office of the Provost, University of Denver.

*The members of the CARE Network are shown in [Appendix E1](#) in this article's Online Repository at www.jacionline.org.

Supported by grants 5U10HL064287, 5U10HL064288, 5U10HL064295, 5U10HL064307, 5U10HL064305, and 5U10HL064313 from the National Heart, Lung, and Blood Institute. This study was carried out in part in the General Clinical Research Centers at Washington University School of Medicine (M01 RR00036) and National Jewish Medical and Research Center (M01 RR00051). This publication was made possible by grant no. UL1 RR024992 from the National Center for Research Resources (NCRR), a component of the National Institutes of Health (NIH), and NIH Roadmap for Medical Research. Its contents are solely the responsibility of the authors and do not necessarily represent the official view of NCRR or NIH.

Disclosure of potential conflict of interest: R. F. Lemanske, Jr, is a speaker for Merck, AstraZeneca, Doernbecher Children's Hospital, Washington University, the Medicus Group, the Park Nicolet Institute, the American College of Allergy, Asthma & Immunology, the LA Allergy Society, the Michigan Allergy/Asthma Society, the Medical College of Wisconsin, the Fund for Medical Research and Education (Detroit), Children's Hospital of Minnesota, the Toronto Allergy Society, the American Academy of Allergy, Asthma & Immunology, Beaumont Hospital (Detroit), the University of Illinois, the Canadian Society of Allergy and Clinical Immunology, and New York Presbyterian; has consultant arrangements with AstraZeneca, Map Pharmaceuticals,

Gray Consulting, Smith Research, the Merck Childhood Asthma Network, Novartis, Quintiles/Innovax, RC Horowitz & Co, and Scienomics; is an author for Up-to-Date; and is a textbook editor for Elsevier. C. A. Sorkness is on the advisory boards for GlaxoSmithKline, Schering-Plough, and AstraZeneca and receives research support from Schering-Plough and Compleware/Sandoz. S. J. Szeffler has consultant arrangements with GlaxoSmithKline, Genentech, Merck, Boehringer Ingelheim, Novartis, and Schering-Plough and receives research support from the National Institutes of Health (NIH)/National Heart, Lung, and Blood Institute (NHLBI) Childhood Asthma Management Program (CAMP), the NHLBI Childhood Asthma Research and Education (CARE), the NIH/NHLBI Asthma Clinical Research Network (ACRN), the NIH/National Institute of Allergy and Infectious Diseases Inner-City Asthma Consortium (ICAC), GlaxoSmithKline, the NIH/NHLBI Asthma Net, and the National Institute of Environmental Health Sciences/Environmental Protection Agency Childhood Environmental Health Center. R. S. Zeiger has consultant arrangements with Aerocrine, AstraZeneca, Genentech, Merck and Co, MedImmune, Sunovion/Sepracor, and Novartis and receives research support from Aerocrine, Genentech, GlaxoSmithKline, and Merck and Co. L. B. Bacharier receives honoraria from AstraZeneca, Genentech, GlaxoSmithKline, Merck, and Aerocrine and serves on advisory boards for GlaxoSmithKline and Schering-Plough. The rest of the authors have declared that they have no conflict of interest.

Received for publication October 28, 2010; revised June 16, 2011; accepted for publication July 13, 2011.

Reprint requests: Caroline C. Horner, MD, Department of Pediatrics, Washington University School of Medicine, St Louis Children's Hospital, One Children's Place, St Louis, MO 63110. E-mail: horner_k@kids.wustl.edu.

0091-6749/\$36.00

© 2011 American Academy of Allergy, Asthma & Immunology

doi:10.1016/j.jaci.2011.07.018

Abbreviations used

ACD: Asthma control day
 NASRA: Nocturnal asthma symptom requiring albuterol
 PACT: Pediatric Asthma Controller Trial
 PEF: Peak Expiratory Flow
 RR: Relative risk

the prevalence of nocturnal asthma,⁶⁻¹¹ associations with nocturnal asthma and sleep quality,¹⁰ and other factors associated with nocturnal asthma,^{9,12-15} but all of these studies were of short duration (≤ 7 days) or cross-sectional. One cross-sectional study examined the consequences of nocturnal asthma on school attendance, school performance, and parents' work attendance by using a parental report for both awakening and morbidity in the 4 weeks before interviews. The authors concluded that nocturnal awakening might affect these outcomes but were not able to examine associations over time because of the cross-sectional design.¹² Fuhlbrigge et al¹⁶ have also shown that the number of nocturnal awakenings over a 4-week period was associated with future asthma-related events (emergency department visits, hospitalizations, or oral steroid bursts).

The Pediatric Asthma Controller Trial (PACT) was a 48-week-long randomized clinical trial involving 6- to 14-year-old children with mild-to-moderate persistent asthma that incorporated measures to enhance and monitor medication adherence.¹⁷ It provides the opportunity to identify the prevalence of and factors related to nocturnal asthma symptoms requiring albuterol (NASRAs), as well as clinically important events linked to these symptoms. To our knowledge, this report is the first examination of prospective data of extended duration to determine associations of NASRAs in children with asthma with the ability to discriminate the consequences of nocturnal asthma symptoms that occur both within and outside periods of exacerbation. Furthermore, it defines the impact of these symptoms on morbidity under study conditions with medications provided and monitored.

METHODS

The details of the trial have been previously described.¹⁷ Briefly, 285 subjects aged 6 to less than 14 years with mild-to-moderate persistent asthma were randomized. Inclusion criteria were physician-diagnosed asthma, PC₂₀ methacholine FEV₁ of 12.5 mg/mL or less, and no personal smoking in the past year. Exclusion criteria were albuterol use (>8 rescue puffs per day on average), symptoms (nighttime awakenings >2 days per week on average), or both consistent with severe persistent disease during the run-in period; FEV₁ of less than 80% of predicted value at screening or less than 70% of predicted value at randomization; 2 or more asthma hospitalizations in the past year; 4 or more courses of systemic corticosteroids in the past year; history of a life-threatening asthma exacerbation; less than 75% adherence to doses of placebo capsules and dry powder inhaler during the 2-week run-in period; and respiratory tract infection, asthma exacerbation, or systemic corticosteroid use within 4 weeks.

Participants demonstrated symptoms consistent with mild-to-moderate persistent asthma during the 2-week run-in period based on diary symptoms, rescue albuterol use, or peak expiratory flow (PEF) of less than 80% calculated from the mean of morning and evening PEFs obtained during the final week of the run-in period at least 3 times per week while not receiving controller medication for at least 2 weeks before randomization. Participants were randomized to one of 3 treatment groups for 48 weeks: (1) 100 μ g of fluticasone propionate administered through a Diskus (GlaxoSmithKline,

Research Triangle Park, NC) twice daily and oral placebo every evening; (2) 100 μ g of fluticasone propionate/50 μ g of salmeterol administered through a Diskus every morning and 50 μ g of salmeterol Diskus every evening (PACT combination) and oral placebo every evening; and (3) placebo administered through a Diskus twice daily and 5 mg of oral montelukast every evening. PEF, symptom scores, and albuterol use for rescue were recorded by a parent or caregiver on diaries twice daily. Older children were permitted to complete diaries with help from a parent or caregiver. Cough and wheeze were scored on a 0- to 3-point scale: 0, no symptoms; 1, mild (awareness of symptoms that were easily tolerated); 2, moderate (symptoms with some discomfort causing some interference of sleep or daily activities); and 3, severe (symptoms that led to inability to sleep or perform daily activities). Each morning, parents were asked to record whether "albuterol was used for asthma during the night." An affirmative response to this question identified a NASRA.

During the trial, oral prednisone was initiated if (1) the participant used more than 12 puffs of albuterol in 24 hours and had a diary card symptom code of 3 or PEF values of less than 70% of personal best before each albuterol use, (2) the subject had a symptom code of 3 for 48 hours or longer, or (3) PEF decreased to less than 50% of personal best despite albuterol treatment or (4) at the physician's discretion. An asthma control day (ACD) was defined as a day without albuterol rescue use, use of oral corticosteroids, use of nonstudy asthma medications, PEF of less than 80% of personal best, daytime symptoms, nighttime awakenings, unscheduled health care visits, emergency department visits, or hospitalizations for asthma and school absenteeism for asthma.

The protocols and consents were approved by the institutional review boards at all participating centers. Parents provided written informed consent, and participants provided written assent. The Childhood Asthma Research and Education Network Data and Safety Monitoring Board monitored the trial.

Statistical analysis

Data analyses were performed by using diary data. One of the subjects did not have diary data recorded after randomization, and therefore data from 284 subjects were analyzed. The primary outcome in PACT was the percentage improvement in ACDs. This percentage improvement was defined by comparing the 48-week treatment period with the run-in placebo period. A full description of the primary statistical analysis plan and sample size justification was previously reported.¹⁷

Determination of NASRAs

Most (88.4%) subjects were followed for 48 weeks because 35 participants withdrew from the study before 48 weeks (no difference in rates between treatment groups). Sixteen participants were lost to follow-up, 7 withdrew consent, and 9 withdrew for other reasons. Participants provided data to this analysis if they completed any diary cards during the study. Only 4 participants had less than 28 days of diary data, and 32 participants had less than 100 days of diary data. Because of the varying amount of diary card data obtained, participant withdrawal, or treatment failure, an annualized frequency of NASRAs was determined as the total number of NASRAs recorded divided by the number of days for which diary data were available multiplied by 365 days. Subjects were stratified into 3 groups based on the annualized frequency of NASRAs during the treatment period: 0, 1 to 12, and 13 or more per year. The 13 annualized NASRAs cut point was chosen because 1 or fewer nocturnal awakening per month represents well-controlled asthma among children 5 to 11 years of age per the National Asthma Education and Prevention Program/Expert Panel Report-3 guidelines.¹ These 3 groups were compared with respect to baseline characteristics by using ANOVA for continuous measures, such as body mass index, age, and lung function parameters, and χ^2 tests for categorical assessments, such as race, sex, and medication history.

Association studies

Longitudinal associations between NASRAs and exacerbations and other diary-based symptom parameters, including cough, wheeze, albuterol use, low PEF, school absenteeism, and doctor contacts were analyzed by using the

TABLE I. Baseline characteristics relating to NASRA frequency

Characteristic	No. of annualized NASRAs			P value
	0 NASRAs (79 subjects)	1-12 NASRAs (136 subjects)	≥13 NASRAs (69 subjects)	
Male sex, no. (%)	50 (63.3)	88 (64.7)	36 (52.5)	NS
BMI (kg/m ²)	19.5 ± 4.0	20.1 ± 4.8	20.3 ± 5.8	NS
Nonwhite race,* no. (%)	13 (16.5)	23 (16.9)	22 (31.2)	.03
Age at randomization (y)	10.0 ± 2.2	9.8 ± 2.3	9.7 ± 2.0	NS
Age at onset of asthma (y)	3.6 ± 2.8	3.1 ± 2.7	3.0 ± 2.7	NS
No. of NASRAs/subject during the 14-d run-in period	0.10 ± 0.3	0.58 ± 1.1	1.3 ± 1.5	<.0001
No. of asthma-free days/subject during the 14-d run-in period	4.7 ± 3.7	3.5 ± 3.0	3.4 ± 3.0	.008
Morning PEF during run-in period (L/min)	252.0 ± 72.0	244.8 ± 71.8	248.6 ± 58.4	NS
Evening PEF during run-in period (L/min)	256.8 ± 69.8	251.9 ± 74.1	254.7 ± 59.1	NS
PEF variability during run-in period (%)	9.3 ± 4.6	10.2 ± 5.8	9.8 ± 4.7	NS
Pre-BD FEV ₁ (% predicted)	98.8 ± 11.2	96.3 ± 12.8	98.3 ± 12.4	NS
Pre-BD FEV ₁ /FVC (%)	80.9 ± 7.5	78.8 ± 7.7	81.3 ± 7.8	NS
Maximum BD response (%)	9.9 ± 7.3	10.9 ± 7.5	11.1 ± 8.3	NS
Peripheral blood eosinophils (%)	5.4 ± 3.6	6.1 ± 4.6	6.4 ± 3.8	NS
PC ₂₀ (mg/mL), median (quartile 1-quartile 3)	1.1 (0.4-2.6)	0.8 (0.3-2.5)	0.8 (2-2.9)	NS
FENO (ppb), median (quartile 1-quartile 3)	24.8 (9.7-50.5)	22.7 (12.8-51.3)	31.9 (12.6-58.0)	NS
IgE (IU/mL), median (quartile 1-quartile 3)	129.0 (40.9-363.0)	164 (61.7-363.0)	176.0 (69.0-415.0)	NS
At least 1 positive skin test result, no. (%)	58 (73.4)	109 (80.2)	55 (79.7)	NS
Medication use in prior year				
Inhaled or nebulized corticosteroids, no. (%)	44 (55.7)	80 (58.5)	36 (52.2)	NS
Fluticasone/salmeterol combination, no. (%)	10 (12.7)	15 (11.4)	10 (13.7)	NS
Montelukast, no. (%)	28 (35.4)	52 (38.2)	15 (21.7)	NS

Data represent means ± SDs, except as noted.

BD, Bronchodilator; BMI, body mass index; FENO, fraction of exhaled nitric oxide; FVC, forced vital capacity.

*Nonwhite race was 73% black, 17% American Indian, 3% Asian, and 7% Pacific Islander.

Cochran-Mantel-Haenszel test stratified by subject. Relative risks (RRs) and associated 95% CIs were also calculated. Associations were also examined stratified by treatment group. All analyses were carried out with the SAS statistical software system, version 9.1 (SAS Institute, Inc, Cary, NC). Significance was established at a 2-sided *P* value of less than .05.

RESULTS

Prevalence and frequency of NASRAs and the effect of controller therapy

Two hundred five (72.2%) of 284 subjects had at least 1 NASRA over the 48-week duration of the trial. One hundred thirty-six (47.9%) subjects had 1 to 12 NASRAs, and 69 (24.3%) subjects had 13 or more NASRAs. Some (31.2%) of the subjects experienced at least 1 NASRA during the 2-week run-in period (maximum of 4 nocturnal awakenings permitted during the run-in period for randomization). The majority (73.5%) of NASRAs occurred on isolated nights without a NASRA occurring on the following night, whereas 14.8% of NASRAs occurred on 2 consecutive nights, and 11.7% of NASRAs occurred on 3 or more consecutive nights. The frequency of NASRAs was greatest in the fall, with nearly double the frequency during the fall compared with the summer (31.5% vs 16.8%, *P* < .0001) and frequencies during the spring (24%) and winter (28%) being intermediate. The frequency of NASRAs was lowest in the fluticasone group (median, 2.0 NASRAs/year; first quartile, 0; third quartile, 7), followed by the PACT combination group (median, 3.0 NASRAs/year; first quartile, 0; third quartile, 13), and highest in the montelukast group (median, 6.5 NASRAs/year; first quartile, 1; third quartile, 18; overall: *P* = .014, fluticasone group vs montelukast group: *P* = .005,

fluticasone group vs PACT combination group: *P* = .11, montelukast group vs PACT combination group: *P* = .16).

Characteristics of subjects with NASRAs

Subjects with 13 or more NASRAs were more likely to be nonwhite than subjects with less than 13 NASRAs (*P* = .03, Table I). The number of NASRAs during the trial was directly associated with the number of NASRAs during the run-in period (*P* < .0001) and inversely related to the number of ACDs experienced during the run-in period (*P* = .008). The number of NASRAs (0, 1-12, and ≥13) did not differ by other baseline characteristics, such as age, sex, controller medication use in the prior year, peripheral blood eosinophil counts, serum IgE levels, skin test positivity, PC₂₀, PEF variability during the run-in period, and exhaled nitric oxide levels at baseline. Only 30 parents reported smoking at study entry, and there was no evidence of association of smoke exposure to NASRAs.

NASRAs and asthma exacerbations

The majority (81.3%) of NASRAs occurred outside of exacerbation periods, which were comprised of intervals including the 7 days before the oral corticosteroid start date, the duration of oral corticosteroid use (typically 4 days), and the 7 days after completion of oral corticosteroids. Only 38.4% of exacerbation periods included 1 or more NASRAs, and when NASRAs were present during the 7 days preceding initiation of prednisone, the frequency was low until the day before prednisone was started (Fig 1). The occurrence of a NASRA was neither a specific nor

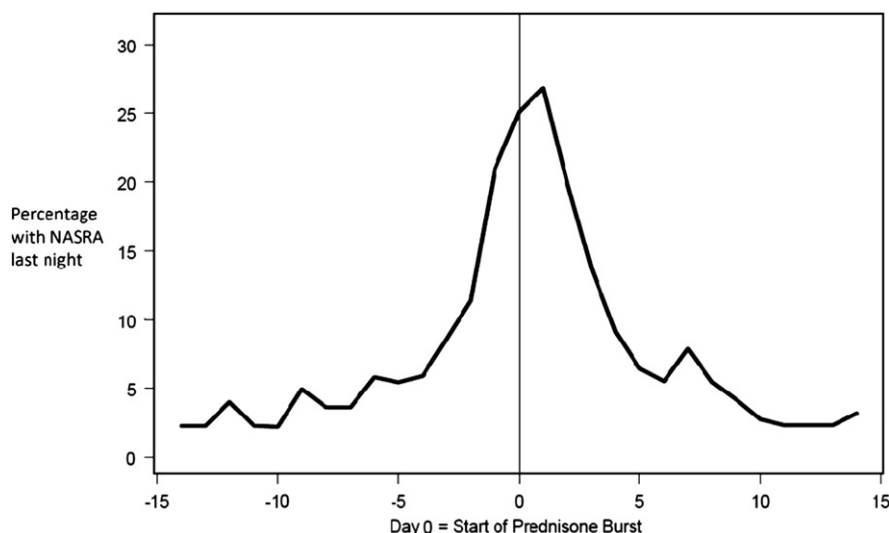


FIG 1. NASRA occurrence during exacerbation periods. The *horizontal axis* is centered on the day prednisone treatment was initiated. For 21% of the asthma exacerbations that occurred during the course of the trial, a NASRA was reported the night before prednisone was initiated. The frequency of NASRAs remained low until the third day before prednisone initiation and returned to pre-exacerbation levels within 5 days.

sensitive indicator of an exacerbation requiring oral corticosteroid (positive predictive value, 0.12).

Symptom changes before occurrence of NASRAs

Although the likelihood of a NASRA increased as symptom severity (cough and wheeze) and use of albuterol for rescue increased, NASRAs were still infrequent after days with significant asthma symptoms: a NASRA occurred during only 19.0%, 17.8%, and 20.5% of nights after daytime reports of severe cough, severe wheeze, or albuterol use of 7 or more puffs, respectively (Tables II-IV). The likelihood of a NASRA was related to the PEF obtained the evening of the NASRA, with a red-zone PEF being followed by a NASRA on 5.9% of nights, whereas a green-zone PEF was followed by a NASRA on 1.4% of nights (Table V and see the [Results](#) section in this article's Online Repository at www.jacionline.org).

Effect of NASRAs on school attendance and doctor contact was greater outside of exacerbations than during exacerbation periods

Albuterol use, school absence, doctor contact, significant wheeze (score of 2 or 3), and significant cough (score of 2 or 3) all occurred significantly more frequently on days after a NASRA than on days preceding a NASRA (Table VI). Overall, the effect of a NASRA was greatest for school absence the following day (RR, 14.9 [95% CI, 12.2-18.4] overall) and least for albuterol rescue use the following day (RR, 2.4 [95% CI, 2.3-2.5] overall) when compared with these events on days that preceded a NASRA. Associations between NASRAs and these indicators of morbidity were present both during and outside exacerbations, with RRs for the effects of NASRAs being greater outside than during exacerbations. Three hundred nine (58.6%) of 527 school absences occurred outside of exacerbation periods. Of these 309 absences, 26.2% included reported NASRAs the prior night, whereas 43.6% of the absences during exacerbation periods

TABLE II. Occurrence and severity of cough during the day preceding a NASRA

Cough score during day	Report of a NASRA that night		
	No NASRAs, no. (%)	NASRAs, no. (%)	
0 (no symptoms)	57,080 (98.6)	802 (1.4)	$P < .0001$
1 (mild)	14,635 (96.4)	540 (3.5)	
2 (moderate)	3,414 (87.8)	477 (12.3)	
3 (severe)	592 (81.0)	141 (19.0)	

no., Number of events for all participants.

TABLE III. Occurrence and severity of wheeze during the day preceding a NASRA

Wheeze score during day	Report of a NASRA that night		
	No NASRAs, no. (%)	NASRAs, no. (%)	
0 (no symptoms)	65,719 (98.3)	1170 (1.7)	$P < .0001$
1 (mild)	7,607 (94.4)	448 (5.6)	
2 (moderate)	2,114 (88.3)	281 (11.7)	
3 (severe)	281 (82.2)	61 (17.8)	

no., Number of events for all participants.

were preceded by a NASRA. Similarly, 237 (53.7%) of 441 doctor contacts occurred outside exacerbation periods. Of these 237 contacts, 25.3% reported NASRAs the prior night, whereas 39.5% of doctor contacts during exacerbation periods were preceded by a NASRA.

DISCUSSION

Over the 48-week treatment period in PACT, during which continuous therapy with controller medication was provided by the study, the vast majority (81.3%) of NASRAs occurred in periods outside of exacerbations. Nights with asthma symptoms

TABLE IV. Occurrence and amount of albuterol use during the day preceding a NASRA

Puffs of albuterol in previous 24 h	Report of a NASRA that night		
	No NASRAs, no. (%)	NASRAs, no. (%)	
0	61,020 (98.6)	851 (1.4)	$P < .0001$
1-2	9,663 (95.0)	499 (5.0)	
3-4	3,296 (91.9)	291 (8.1)	
5-6	1,006 (88.6)	129 (11.4)	
≥7	736 (79.5)	190 (20.5)	

no., Number of events for all participants.

TABLE V. Evening PEF and the occurrence of a NASRA that night

Evening PEF zone	Report of a NASRA that night		
	No NASRAs, no. (%)	NASRAs, no. (%)	
Green	60,259 (98.6)	858 (1.4)	$P < .0001$
Yellow	10,680 (96.1)	437 (3.9)	
Red	286 (94.1)	18 (5.9)	

no., Number of events for all participants.

requiring albuterol use were often followed the next day by indicators of asthma morbidity, including increased albuterol use, school absence, doctor contact, and occurrence of severe wheeze, cough, or both. The RRs of occurrence of these indicators of morbidity caused by NASRAs outside of exacerbations were greater than the corresponding RRs within periods of exacerbation, indicating that nocturnal asthma symptoms have a substantial clinical impact on patients' lives, even during periods of relative asthma stability (ie, not during exacerbation). To our knowledge, such a pattern of nocturnal asthma symptom morbidity has not previously been reported, in part because of the cross-sectional approaches of prior studies.^{12,15}

Nearly a quarter of participants with mild-to-moderate persistent asthma receiving daily controller therapy experienced a NASRA on at least a monthly basis, with the distribution of NASRAs similar to the seasonal distribution of exacerbations (greatest in fall and lowest in summer).¹⁸ Treatment group assignment significantly affected the occurrence of NASRAs, with the fluticasone group having a significantly lower rate of NASRAs than the montelukast group. The superiority of fluticasone in reducing NASRAs is consistent with the overall effect of fluticasone in terms of ACDs reported in a previous PACT publication.¹⁷ Similar to the findings in terms of ACDs, the PACT combination of 50 µg of salmeterol twice daily with 100 µg of fluticasone once daily in the morning was not associated with significantly fewer NASRAs than fluticasone twice daily, despite the use of a long-acting β-agonist in the evening. This finding might have been due to the once-daily (morning) dosing of fluticasone during the trial in the combination group rather than the typical twice-daily dosing of fluticasone. Although salmeterol has been demonstrated to decrease nocturnal awakenings in adults with asthma,¹⁹ the clinical efficacy of salmeterol on nocturnal asthma symptoms might differ in children. The inhaled corticosteroid dosing regimen in the combination group did not allow us to examine whether the nocturnal administration of inhaled corticosteroid would have resulted in a greater effect on nocturnal symptoms.

NASRAs were neither specific nor sensitive indicators nor antecedents of exacerbations requiring oral corticosteroid. Even

when NASRAs did occur during the week preceding an exacerbation, they generally did not appear until a couple of nights before the start of oral corticosteroids (Fig 1). Similarly, PEFs, symptoms, and albuterol use during the day were not good indicators of a NASRA that evening because only about 6% of evenings with a red-zone PEF were followed by a NASRA, and only about 20% of days before a NASRA included severe cough or wheeze or 7 or more puffs of albuterol use. Only 38.4% of exacerbation periods included a report of at least 1 NASRA, suggesting that NASRAs are a sign of symptom escalation in a subgroup of subjects.

Parents appear to seek medical attention after some, but not all, NASRAs, and NASRAs that occur during exacerbations were more often followed by a doctor's office visit. This might be due to the cumulative nature of the symptoms that occur with the exacerbation and a higher likelihood that symptoms during exacerbations might be more severe or less responsive to therapy than those outside of exacerbation periods.

The Childhood Asthma Management Program trial of children with mild-to-moderate asthma reported the prevalence of at least 1 nocturnal awakening during the 28-day albuterol-only and exacerbation-free run-in period to be 33.7%,⁸ a finding very similar to the 31.2% of subjects who experienced at least 1 NASRA during the 2-week PACT albuterol-only run-in period and not much dissimilar to the 24.3% who had 13 or more NASRAs during PACT while taking a controller medication. The current analysis expands on the results from the Childhood Asthma Management Program because it includes a longer period of observation (48 vs 4 weeks), as well as examining NASRAs that occur both outside and during asthma exacerbations and examining the effects of different treatment regimens on these events. To our knowledge, these observations have not been previously reported in either adults or children.

A limitation of this study is that the diary card did not include separate questions for nocturnal awakenings and nocturnal albuterol use for asthma symptoms. NASRAs are likely a suitable surrogate measure of nocturnal awakenings because albuterol use requires being awake. However, our data might underestimate nocturnal awakenings because some nocturnal awakenings might not have been treated with albuterol. The study did not include a placebo group to establish the background frequency of NASRAs. Because subjects with very frequent NASRAs during the run-in period were excluded from the trial, the trial might have selected for children with fewer NASRAs. The education provided by the coordinators and the support from the clinical center teams might have influenced clinical events occurring in days after NASRAs, most likely by decreasing event occurrence. It is possible that some patients experienced poor perception of airflow obstruction and thus did not experience a NASRA. Finally, as with all *post hoc* subgroup analyses, inadequate statistical power might have resulted in failure to detect significant associations with NASRAs.

In conclusion, most NASRAs occurred outside exacerbation periods, and those NASRAs observed during exacerbation periods did not appear to be a clinically useful antecedent of exacerbations. Despite the lack of association with exacerbations, NASRAs were associated with morbidity in the form of symptom scores, additional albuterol use, and school absences and doctor contacts outside of exacerbation periods. NASRA frequency appears differentially responsive to controller therapy, with the fluticasone group experiencing the lowest frequency of NASRAs and the montelukast group experiencing the greatest frequency. Because

TABLE VI. Stratified RRs for morbidity on days after and not after a NASRA

Morbidity	Days with a NASRA during previous night	Days without a NASRA during previous night	Stratified RR (95% CI)
Used albuterol			
Overall	58.9% (1,175/1,996)	19.2% (14,882/77,476)	2.4 (2.3-2.5)
During exacerbation	67.6% (252/373)	47.0% (1,345/2,862)	1.7 (1.5-1.8)
Outside exacerbation	56.9% (923/1,623)	18.1% (13,637/74,614)	2.3 (2.2-2.4)
School absence			
Overall	8.8% (176/1,996)	0.5% (351/77,476)	14.9 (12.1-18.4)
During exacerbation	25.5% (95/373)	4.3% (123/2,862)	5.5 (4.0-7.4)
Outside exacerbation	5.0% (81/1,623)	0.3% (228/74,614)	10.6 (7.8-14.4)
Contacted doctor for asthma			
Overall	7.1% (141/1,996)	0.4% (300/77,476)	13.3 (10.5-16.7)
During exacerbation	21.7% (81/373)	4.3% (124/2,862)	4.9 (3.6-6.7)
Outside exacerbation	3.7% (60/1,623)	0.2% (177/74,614)	8.8 (6.1-12.5)
Wheeze score of 2 or 3			
Overall	20.4% (407/1,996)	3.1% (2,400/77,476)	5.8 (5.2-6.4)
During exacerbation	36.2% (135/373)	10.5% (301/2,862)	3.5 (2.9-4.2)
Outside exacerbation	16.8% (272/1,623)	2.8% (2,099/74,614)	5.1 (4.5-5.8)
Cough score of 2 or 3			
Overall	33.8% (675/1,996)	5.2% (4,040/77,476)	6.0 (5.6-6.5)
During exacerbation	61.7% (230/373)	20.6% (590/2,862)	2.9 (2.6-3.3)
Outside exacerbation	27.4% (445/1,623)	4.6% (3,450/74,614)	5.3 (4.8-4.9)

NASRAs were associated with clinically relevant outcomes and treatment differences, inclusion of nocturnal symptoms as an important outcome measure in future clinical trials, along with further investigation into the causes and prevention of nocturnal asthma symptoms, might have substantial clinical implications.

Clinical implications: Nocturnal asthma symptoms primarily occurred outside of exacerbation periods and were associated with clinical morbidity. Investigation into the causes and prevention of childhood nocturnal symptoms might have substantial clinical implications.

REFERENCES

- Expert Panel Report 3 (EPR-3): guidelines for the diagnosis and management of asthma—summary report 2007. *J Allergy Clin Immunol* 2007;120(suppl):S94-138.
- Calhoun WJ. Nocturnal asthma. *Chest* 2003;123(suppl):399S-405S.
- Sutherland ER. Nocturnal asthma. *J Allergy Clin Immunol* 2005;116:1179-87.
- Sutherland ER. Nocturnal asthma: underlying mechanisms and treatment. *Curr Allergy Asthma Rep* 2005;5:161-7.
- Shigemitsu H, Afshar K. Nocturnal asthma. *Curr Opin Pulm Med* 2007;13:49-55.
- Stores G, Ellis AJ, Wiggs L, Crawford C, Thomson A. Sleep and psychological disturbance in nocturnal asthma. *Arch Dis Child* 1998;78:413-9.
- Sadeh A, Horowitz I, Wolach-Benodis L, Wolach B. Sleep and pulmonary function in children with well-controlled, stable asthma. *Sleep* 1998;21:379-84.
- Strunk RC, Sternberg AL, Bacharier LB, Szeffler SJ. Nocturnal awakening caused by asthma in children with mild-to-moderate asthma in the Childhood Asthma Management Program. *J Allergy Clin Immunol* 2002;110:395-403.
- Ng Man Kwong G, Das C, Proctor AR, Whyte MK, Primhak RA. Diagnostic and treatment behaviour in children with chronic respiratory symptoms: relationship with socioeconomic factors. *Thorax* 2002;57:701-4.
- Chugh IM, Khanna P, Shah A. Nocturnal symptoms and sleep disturbances in clinically stable asthmatic children. *Asian Pac J Allergy Immunol* 2006;24:135-42.
- Mustafa G, Khan PA, Iqbal I. Nocturnal asthma in school children of south Punjab, Pakistan. *J Ayub Med Coll Abbottabad* 2008;20:36-9.
- Diette GB, Markson L, Skinner EA, Nguyen TT, Algatt-Bergstrom P, Wu AW. Nocturnal asthma in children affects school attendance, school performance, and parents' work attendance. *Arch Pediatr Adolesc Med* 2000;154:923-8.
- Landstra AM, Postma DS, Boezen HM, van Aalderen WM. Role of serum cortisol levels in children with asthma. *Am J Respir Crit Care Med* 2002;165:708-12.
- Landstra AM, Boezen HM, Postma DS, van Aalderen WM. Effect of intravenous hydrocortisone on nocturnal airflow limitation in childhood asthma. *Eur Respir J* 2003;21:627-32.
- Fiese BH, Winter MA, Sliwinski M, Anbar RD. Nighttime waking in children with asthma: an exploratory study of daily fluctuations in family climate. *J Fam Psychol* 2007;21:95-103.
- Fuhlbrigge AL, Weiss ST, Kuntz KM, Paltiel AD. Forced expiratory volume in 1 second percentage improves the classification of severity among children with asthma. *Pediatrics* 2006;118:e347-55.
- Sorkness CA, Lemanske RF Jr, Mauger DT, Boehmer SJ, Chinchilli VM, Martinez FD, et al. Long-term comparison of 3 controller regimens for mild-moderate persistent childhood asthma: the Pediatric Asthma Controller Trial. *J Allergy Clin Immunol* 2007;119:64-72.
- Covar RA, Szeffler SJ, Zeiger RS, Sorkness CA, Moss M, Mauger DT, et al. Factors associated with asthma exacerbations during a long-term clinical trial of controller medications in children. *J Allergy Clin Immunol* 2008;122:741-7, e4.
- Kraft M, Wenzel SE, Bettinger CM, Martin RJ. The effect of salmeterol on nocturnal symptoms, airway function, and inflammation in asthma. *Chest* 1997;111:1249-54.

RESULTS

PEF as a predictor of NASRAs

The majority (73.5%) of NASRAs occurred on isolated nights without a NASRA occurring on either the preceding or following night. Some (14.8%) NASRAs were followed by a NASRA the subsequent night, and 11.7% of NASRAs were followed by NASRAs during the next 2 consecutive nights. Peak flow measures the evening after a NASRA were associated with an increased risk of a consecutive NASRA. The occurrence of a non-green-zone PEF on the evening after a NASRA was frequently followed by a second consecutive NASRA. A red-zone PEF on the evening after a NASRA was followed by a second consecutive NASRA on 56.1% of nights, a yellow-zone PEF was followed by a consecutive NASRA on 45.4% of nights, and a green-zone PEF was followed by a consecutive NASRA on 27.1% of nights ($P < .0001$). Consecutive NASRAs were 5 times more likely (odds ratio, 5; 95% CI, 2.1-12.0) if a red-zone PEF was noted the evening after the initial NASRA compared with a green-zone PEF.

APPENDIX E1

The members of the CARE Network as of October 2002 are as follows:

Clinical Centers

National Jewish Medical and Research Center, Denver, Colo: Stanley J. Szeffler, MD (Principal Investigator); Gary Larsen, MD (Co-Investigator); Joseph Spahn, MD (Co-Investigator); Ronina Covar, MD (Co-Investigator); Andrew Liu, MD (Co-Investigator); Neal Jain, MD (Study Physician); Harvey Leo, MD (Study Physician); Beth Macomber, MD (Study Physician); Chris Mjaanes, MD (Study Physician); Ben Song, MD (Study Physician); D. Sundström (Coordinator); Keith Breese (Coordinator); Michael White (Research Assistant); Kate Morgan (Coordinator); Amy Grumann, RN (Coordinator); Gayle Spears, PA-C (Referring Physician Assistant); Jay Markson, MD (Referring Pediatrician); Jeffrey Barter, MD (Referring Pediatrician); Melanie Phillips (Coordinator); Katie Patterson (Coordinator).

University of Wisconsin, Clinical Science Center, Madison, Wis: Christine A. Sorkness, PharmD, (Principal Investigator); Robert F. Lemanske, Jr, MD (Co-Investigator); Mark H. Moss, MD (Co-Investigator); Marzena E. Krawiec, MD (Co-Investigator); David B. Allen, MD (Consultant); Kristen Blotz, RN (Coordinator); Sarah Garibay, RN (Coordinator); Kelly Miller (Coordinator); Holly Eversoll, RN (Coordinator); Alana Clark (Coordinator); Kathleen Kelly Schanovich, NP (Coordinator); Rick Kelley (Pulmonary Function Manager).

University of California San Diego Medical Center and Kaiser Permanente Allergy Center, San Diego, Calif: Robert S. Zeiger, MD, PhD (Principal Investigator); Gregory Heldt, MD (Co-Investigator); Michael H. Mellon, MD (Co-Investigator); Michael Schatz, MD (Co-Investigator); Noah J. Friedman, MD (Co-Investigator); Sandra C. Christiansen, MD (Co-Investigator); Alfredo A. Jalowayski, PhD (Co-Investigator); Hal Hoffman, MD (Co-Investigator); Kathleen Harden, RN (Coordinator); Catherine Nelle, RN (Coordinator); Eva Rodriguez, RRT; Elaine Jensen; Linda Galbreath.

Washington University School of Medicine, St Louis, Mo: Robert C. Strunk, MD (Principal Investigator); Leonard B. Bacharier, MD (Co-Investigator); Gordon R. Bloomberg, MD (Co-Investigator); James M. Corry, MD (Co-Investigator); Tina Oliver-Welker, CRTT, CAE (Coordinator); Valerie Morgan,

RRT (Coordinator); Kevin Hodgdon, RRT, CPFT (Coordinator); Wanda Caldwell, RRT, MBA (Coordinator); Debbie Pirrello, RRT-NPS; Cindy Moseid (Secretary).

Arizona Respiratory Center, University of Arizona, College of Medicine, Tucson, Ariz: Fernando D. Martinez, MD (Principal Investigator); Wayne J. Morgan, MD (Co-Investigator); Theresa W. Guilbert, MD (Co-Investigator); John D. Mark, MD (Co-Investigator); and Mark A. Brown, MD (Co-Investigator); James Goodwin, PhD (Coordinator); Melisa Celaya (Coordinator); Anna Valencia (Coordinator); Janet Lawless, FNP; Rosemary Weese, RN; Shelley Radford, RT; William Hall, RT.

Resource Centers

Chair's Office, National Jewish Medical and Research Center, Denver, Colo: Lynn M. Taussig, MD (Study Chair).

Project Office, National Heart, Lung and Blood Institute, Bethesda, Md: James Kiley, PhD, (Director of the NHLBI Division of Lung Diseases); Virginia Taggart, MPH (NHLBI Project Scientist); Gail Weinmann MD (Executive Secretary, DSMB); Gang Zheng, PhD.

Data Coordinating Center, Penn State University College of Medicine, Hershey, Pa: Vernon M. Chinchilli, PhD (Principal Investigator); David Mauger, PhD (Co-Investigator); Ian Paul, MD (Co-Investigator); Gavin Graff, MD (Co-Investigator); Sue Boehmer, Scientific Coordinator; Brenda Phillips (Scientific Coordinator); Loretta Doty (Project Coordinator); Anne-Marie Dyer; Lindsay Texter; Jim Schmidt; Patsy Rawa; Linda Ferrari; Sherrie Whisler; Pamela Arminavage; Brenda Beers; Linda Miller; Judy Potteiger; Lori Schell; Stephanie Olexovitch; Vanessa Simmons; Thuy Tran; Lincoln Milner; Brian Moore; Andrew Sutton.

Committees

Data and Safety Monitoring Board: Thomas F. Boat, MD (Chair), Children's Hospital Medical Center, Cincinnati, Ohio; William C. Bailey, MD, University of Alabama at Birmingham, Birmingham, Ala; Mary Kay Garcia, PhD, RN, CPNP; Carolyn M. Kercsmar, MD, Case Western Reserve University, Cleveland, Ohio; Lester Lyndon Key, Jr, MD, Medical University of South Carolina, Charleston, SC; James Tonascia, PhD, Johns Hopkins University, Baltimore, Md; Benjamin Wilfond, MD, National Human Genome Research Institute, Bethesda, Md.

Protocol Review Committee: Philip Ballard, MD, PhD (Chair), Children's Hospital of Philadelphia, Philadelphia, Pa; Clarence E. Davis, PhD, University of North Carolina, Chapel Hill, NC; Diane E. McLean, MD, PhD, MPH, New York State Psychiatric Institute, New York, NY; Gail Shapiro, MD, Asthma, Inc, Seattle, Wash; Paul O'Byrne, MD, St Joseph's Hospital, Hamilton, Ontario, Canada; Mark Liu, MD, Johns Hopkins Asthma and Allergy Center, Baltimore, Md.

Executive Committee: Lynn M. Taussig, MD (Chair); Virginia S. Taggart, MPH; Stanley J. Szeffler, MD; Robert F. Lemanske, Jr, MD; Robert S. Zeiger, MD, PhD; Robert C. Strunk, MD; Fernando D. Martinez, MD; Vernon M. Chinchilli, PhD.

Publication and Presentation Committee: Robert F. Lemanske, Jr, MD (Chair); Stanley J. Szeffler, MD; Fernando D. Martinez, MD.

Quality Control Committee: Robert S. Zeiger, MD, PhD (Chair); Vernon M. Chinchilli, PhD; Christine A. Sorkness, PharmD; Robert C. Strunk, MD; Theresa Guilbert, MD; Dave Mauger, PhD; Stanley Szeffler, MD; Brenda Phillips, MS; D. Sundström; James Schmidt, BS; Kristen Blotz, RN; Sarah Garibay, RN; Kelly Miller.

Equipment Committee: Wayne Morgan, MD (Chair); Gregory Heldt, MD; Gary Larsen, MD; Christine A. Sorkness, PharmD; Joseph D. Spahn, MD; Gavin Graff, MD; Kevin Hodgdon; Rick Kelley; Shelley Radford; Eva Rodriguez, Melanie Phillips; Brenda Phillips; Loretta Doty; Richard Evans; Jason Lennon, Lori Sanders, Venus Grella, Linda Ferrari.

Genetics Committee: Fernando D. Martinez, MD (Chair); Stanley J. Szeffler, MD; Robert F. Lemanske, Jr, MD; Vernon M. Chinchilli, PhD; David T. Mauger, PhD; Brenda Phillips, MS.

Pharmaceutical Suppliers

GlaxoSmithKline, Inc, Research Triangle Park, NC, donated the Flovent Diskus, the Serevent Diskus, the Advair Diskus, and albuterol.

Equipment and Materials Support

Lincoln Diagnostics (Multi-Test II kits, donated), Decatur, Ill; MEMS, Medication Event Monitoring Systems, AARDEX, Zug, Switzerland; Aerocrine, Inc, Chicago, Ill; VIASYS Healthcare GmbH, Hoechberg, Germany; Methapharm, Coral Springs, Fla.