

Intranasal mometasone furoate therapy for allergic rhinitis symptoms and rhinitis-disturbed sleep

Eli O. Meltzer, MD*; Dominic A. Munafo, MD†; Weiyuan Chung, MS‡; Gokul Gopalan, MD‡; and Santosh T. Varghese, MD‡

Background: Allergic rhinitis (AR) and related nasal congestion cause rhinitis-disturbed sleep (RDS). Intranasal corticosteroids reduce nasal congestion and improve sleep quality in AR but have not been extensively studied in RDS.

Objective: To evaluate the efficacy of mometasone furoate nasal spray (NS) on nasal symptoms, nasal patency, sleep variables, quality of life, and daytime functioning in perennial AR (PAR) and concomitant RDS.

Methods: In this double-blind 4-week study, 30 adults with PAR and moderate RDS were randomized 2:1 to receive mometasone furoate NS, 200 μ g, or placebo each morning. The primary end point was the apnea-hypopnea index. Secondary outcome measures included changes in total nasal symptom score (TNSS), nighttime symptom score, daytime peak nasal inspiratory flow, nighttime flow limitation index, Rhinoconjunctivitis Quality of Life Questionnaire–Standardized (RQLQ-S) score, Epworth Sleepiness Scale score, and Work Productivity and Activities Impairment–Allergy Specific (WPAI–AS) questionnaire score. Analysis of covariance was used for all efficacy end points.

Results: The apnea-hypopnea index at study end was not statistically significantly different between groups. However, mometasone furoate NS therapy significantly improved morning ($P = .04$) and evening ($P = .01$) TNSSs, morning ($P = .049$) and evening ($P = .03$) nasal obstruction/blockage/congestion, daily peak nasal inspiratory flow ($P = .03$), flow limitation index ($P = .02$), Epworth Sleepiness Scale score ($P = .048$), RQLQ-S score ($P = .03$), and 2 of 5 WPAI–AS domains. Among patients receiving mometasone furoate NS, TNSS improvements were significantly correlated with improved work- and non-work-related productivity.

Conclusions: In patients with PAR and RDS, mometasone furoate NS use improved nasal symptoms, sleepiness, and impairment in daily activities. Correlated reduced nasal symptoms and improved performance suggest that improving AR symptoms with mometasone furoate NS administration can benefit sleep and daytime functioning.

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INTRODUCTION

In the Allergies in America survey^{1,2} of 2,500 adults with allergic rhinitis (AR), congestion was rated as the most bothersome symptom; 60% of participants reported that it was the worst symptom during peak allergy periods. Sleep disturbances are common in congested patients with AR,^{3,4} and significant correlations between morning congestion and sleep impairment have been reported.⁵ Reduced sleep quality

in patients with AR can lead to excessive daytime sleepiness and impaired productivity, quality of life (QOL), memory, mood, and sexuality.⁶ Recent analyses suggest that congestion predicts sleep quality and other key patient-related outcomes⁷ and that improvement in congestion strongly correlates with improved patient outcomes.⁸

Rhinitis-disturbed sleep (RDS), a prevalent problem with substantial effect on patients' daily lives, is defined as subjective sleep impairment coincident with symptomatic AR; its mechanisms are not fully understood.^{4,9} Cytokines and other allergic mediators influence sleep dynamics and daytime sleepiness,¹⁰ and AR symptoms per se may also cause cortical arousal and sleep fragmentation.¹¹ In 1 AR trial,¹² treatment improved rhinorrhea and sleep quality but not other nasal symptoms, suggesting also the role of rhinorrhea in sleep impairment.

Congestion purportedly leads to pharyngeal airway obstruction.¹³ Airway collapse occurs when intraluminal pressure drops below pressure in the surrounding tissues.^{14,15} Increased pharyngeal airway resistance during sleep is characteristic of sleep-disordered breathing (SDB), an underdiagnosed condition especially associated with obesity and aging.^{13,16,17} Obstructive sleep apnea syndrome (OSAS), the

Affiliations: * Allergy and Asthma Medical Group and Research Center, San Diego, California; † Sleep Data Inc and University of California, San Diego, California; ‡ Schering Corp, a division of Merck & Co Inc, Kenilworth, New Jersey.

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most common form of SDB, is characterized by complete (apnea) and incomplete (hypopnea) airway obstruction,^{15,18} most frequently in the oropharynx.¹⁹

Congestion, which reduces nasal airflow and, therefore, airway pressure (via the Bernoulli effect), may increase the likelihood of pharyngeal collapse in mechanically vulnerable regions^{9,20} and precipitate obstruction in susceptible individuals.²¹ Some studies^{21,22} have reported increased risk of OSAS in individuals with AR-related congestion; however, no direct correlation between nasal airflow and apnea-hypopnea frequency has been observed.²³ Patients with AR may also experience impaired sleep without airway obstruction, suggesting that RDS and OSAS are distinct conditions that may have synergistic effects on sleep in some individuals but coexist independently in others. Thus, some patients have only RDS from nasal congestion, other patients with upper airway obstruction may experience only OSAS from pharyngeal blockage, and individuals with RDS and OSAS may have additive effects of both conditions.

Studies^{24,25} in patients with perennial AR (PAR) have shown that intranasal corticosteroids significantly reduce nasal congestion and improve sleep and daytime somnolence. Mometasone furoate nasal spray (NS) is indicated to treat nasal symptoms in seasonal AR (SAR) and PAR. Mometasone furoate NS, 200 µg administered once daily, has been found to significantly improve daytime and nighttime total nasal symptom scores (TNSSs) and individual nasal symptoms, including congestion,²⁶⁻²⁸ and even the most severe nasal symptoms.²⁹ However, no studies, to our knowledge, have reported the efficacy of mometasone furoate NS in improving airway obstruction during sleep in individuals with PAR and RDS.

This study evaluated the efficacy of mometasone furoate NS use in moderate to severe PAR, with or without coexisting SAR, and with historically at least moderately compro-

mised sleep presumed to be from AR, ie, RDS. The study goal was to assess changes in nasal symptoms, nasal airflow, and airway obstruction during sleep in response to mometasone furoate NS treatment. In addition, the effects of mometasone furoate NS use on daytime somnolence, QOL, and daytime functioning were examined.

METHODS

Study Design

A 28-day, randomized, double-blind, placebo-controlled, parallel-group, single-center study was performed in the United States in accordance with the Declaration of Helsinki and guidelines for Good Clinical Practice (Fig 1). The study protocol and the statement of informed consent were reviewed and approved by the Sterling Institutional Review Board, Atlanta, Georgia.

The inclusion and exclusion criteria are listed in Table 1. Patients rated nasal symptoms (obstruction/blockage/congestion, drainage [anterior/posterior], nasal itch, and sneezing) on a scale from 0 (none) to 6 (very severe). The TNSS equaled the summed individual nasal symptom scores. Patients rated subjective sleep interference on a 4-point Likert scale (0, none: no interference at all; 1, mild: not annoying or troublesome, adequate amount of sleep; 2, moderate: rhinitis symptoms interfered somewhat with sleep, awoke a few times; and 3, severe: substantial interference with sleep caused by rhinitis symptoms).

Patients who met the screening visit (visit 1) eligibility criteria entered a 10- to 14-day screening period during which an unattended home sleep study was performed using the Embletta® portable multichannel sleep recorder (Embla, Broomfield, Colorado). Airflow was determined from the nasal pressure signal via a nasal cannula, snoring by frequency filtration of the nasal cannula pressure signal, and

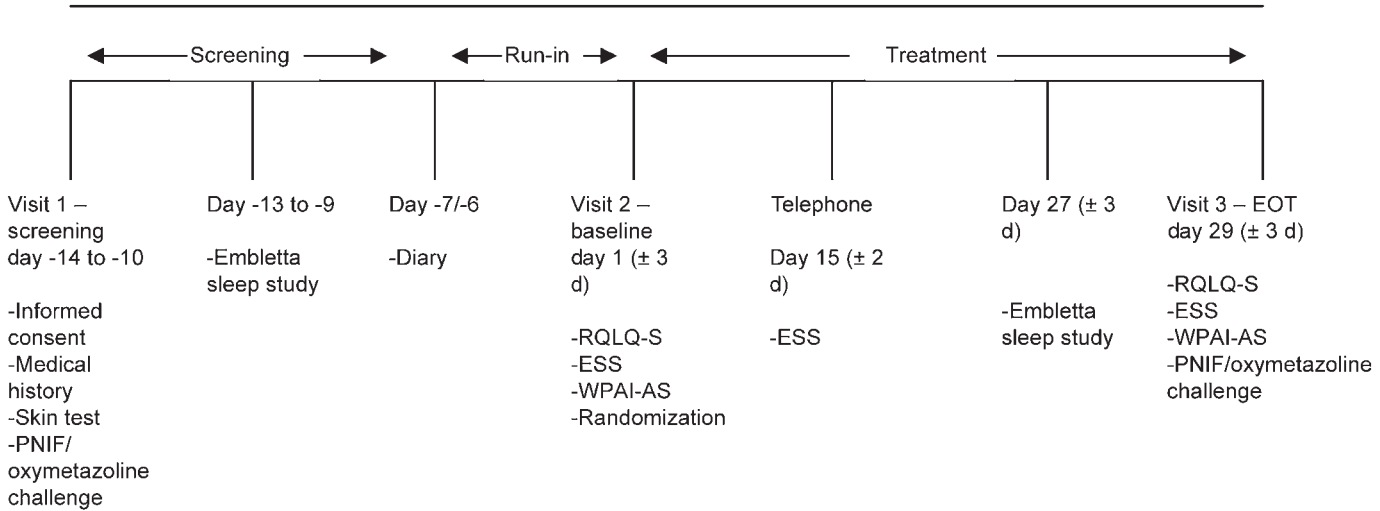


Figure 1. Study design. EOT indicates end of treatment; ESS, Epworth Sleepiness Scale; PNIF, peak nasal inspiratory flow; RQLQ-S, Rhinoconjunctivitis Quality of Life Questionnaire–Standardized; and WPAI–AS, Work Productivity and Activities Impairment–Allergy Specific.

Table 1. Inclusion and Exclusion Criteria

Inclusion criteria	Exclusion criteria
Individuals aged 18-60 y, either sex, and any race	Current use of medication for PAR or treatment during the 10 d before screening with antihistamines or intranasal corticosteroids
≥2-y history of PAR with or without SAR and self-reported sleep disturbances	Presence/history of clinically significant sinusitis, chronic purulent postnasal drip, rhinitis medicamentosa, or respiratory tract or sinus infection
Positive skin prick test reaction to a relevant perennial allergen in the previous 12 mo	Nasal septum ulcers, nasal surgery, nasal trauma, or structural abnormalities, including nasal polyps and septum deviation, that significantly interfere with nasal airflow
Nasal congestion score ≥4 of 6 and TNSS ≥12 of 24 at screening (visit 1) ^a and baseline (visit 2) ^b	Bronchial asthma uncontrolled by short-acting β_2 -adrenergic receptor agonists
Sleep disturbance symptoms and score ≥2 (moderate severity) on the Interference with Sleep Scale at screening (visit 1) ^a and baseline (visit 2) ^c	Morbid obesity (BMI ≥40)
≥5 to ≤30 apnea and hypopnea events per hour during screening	Immunotherapy (desensitization) unless on a stable maintenance schedule and not administered ≤24 h of a study visit
	Night-shift workers who did not adhere to a standard day/night awake/asleep cycle

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); PAR, perennial allergic rhinitis; SAR, seasonal allergic rhinitis; TNSS, total nasal symptom score.

^a During the previous 7 days. Symptom scores were assessed as reflective during the previous 12 hours.

^b On at least 6 of the 15 recordings during the run-in period.

^c On at least 4 of the 8 daily assessments during the run-in period.

respiratory effort by 2 respiratory impedance plethysmography belts around the chest and abdomen. Oxygen saturation and heart rate were derived using a pulse oximeter placed on a finger. Body position and movement were determined using an internal sensor (accelerometer). Apnea was defined as airflow below 10% of baseline for at least 10 seconds. Hypopnea was defined as airflow or respiratory effort of at least 10% but less than 50% of baseline for at least 10 seconds and associated with oxygen desaturation of at least 3%. The apnea-hypopnea index (AHI) was expressed as the average number of apnea plus hypopnea events per hour. Patients in whom the AHI was at least 30 during screening were excluded. The flow limitation index (FLI), a measure of nocturnal upper airway resistance expressed as the percentage of flow-limited breaths, was derived from the nasal pressure signal.³⁰

At the baseline visit (treatment day 1), patients completed the Rhinoconjunctivitis Quality of Life Questionnaire–Standardized (RQLQ-S), the Epworth Sleepiness Scale (ESS), and the Work Productivity and Activities Impairment–Allergy Specific (WPAI-AS) questionnaire. Patients who continued to meet the eligibility criteria were randomized in a 2:1 ratio to receive mometasone furoate NS, 200 μ g, or placebo NS once daily in the morning.

Patients recorded nasal signs and symptoms reflectively (experienced during the previous 12 hours) as described previously herein for the run-in period using diary cards once in the morning within 30 minutes of awakening and once in the evening, approximately 12 hours later. Diary cards were also used to record nighttime symptom score (NSS), including 3 domains (difficulty going to sleep, nighttime awakenings, and nasal congestion on awakening) on a 4-point scale (0 = none to 3 = severe) once in the morning. Peak nasal inspiratory flow (PNIF) measurements were made before

morning dosing and were repeated approximately 12 hours later using an In-Check portable nasal flow meter (Clement Clarke International Ltd, Harlow, England). On day 15, the ESS was completed again via telephone follow-up. On day 27, the Embletta home sleep study was again performed. At a final end-of-treatment (EOT) visit on day 29, patients repeated the RQLQ-S, ESS, and WPAI-AS questionnaire, and, as at screening, a PNIF/oxymetazoline challenge test was performed. Compliance was evaluated throughout the study by asking the patients whether all medications had been taken as instructed and by reviewing diaries for time of medication use.

Safety Assessments

Safety assessments included, but were not limited to, adverse event reports. Details of all reported adverse events and their relationship to the study drug were recorded, along with severity (mild, moderate, severe, or life-threatening) and any action or outcome (eg, hospitalization or discontinuation of therapy).

Statistical Methods

The primary end point was the difference between the mometasone furoate NS and placebo groups in AHI from screening to EOT in the intention-to-treat population (all randomized patients who took at least 1 dose of study medication after the start of treatment and who had a baseline value and ≥1 postbaseline value). Key secondary end points included differences between EOT and baseline measurements of (1) PAR symptoms (TNSS and NSS), (2) daytime and nighttime airflow (PNIF and FLI), (3) QOL measurements (ESS, RQLQ-S, and WPAI-AS), (4) response to oxymetazoline challenge, and (5) number of snoring episodes per hour and snoring time, measured during home sleep monitoring. Com-

parisons were performed using an analysis of covariance model and adjusting for the baseline primary end point and secondary end points that had a baseline value. Daily (morning and evening) scores for nasal symptoms and PNIF were the average of morning and evening scores.

In a post hoc analysis, correlations between changes in (1) TNSS and job impairment, (2) NSS and job impairment, (3) TNSS and daily activity, and (4) NSS and daily activity were examined by means of Pearson correlation coefficient analyses.

RESULTS

Patient Disposition and Characteristics

Thirty patients were randomized to receive mometasone furoate NS (n = 20) or placebo (n = 10). All the patients completed treatment. Final study procedures were not performed for 1 patient in the placebo group who was simulta-

neously participating in another study. The baseline demographic characteristics of the 2 treatment groups showed some mild imbalances (Table 2).

Efficacy End Points

Results of the primary and secondary end points are summarized in Tables 3 and 4 and in Figures 2 through 6. The mometasone furoate NS and placebo groups exhibited similar mild increases in AHI from baseline to EOT (0.96 vs 1.61, $P = \text{NS}$ for mometasone furoate NS vs placebo).

Treatment with mometasone furoate NS resulted in significantly greater improvement in daily (morning and evening) TNSS, nasal obstruction/blockage/congestion, nasal drainage, and sneezing vs placebo use ($P < .05$ for all) (Fig 2). Mometasone furoate NS use was significantly superior to placebo use in morning and evening TNSS. Treatment with

Table 2. Baseline Demographic Characteristics of Each Treatment Group

Characteristic	MFNS group (n = 20)	Placebo group (n = 9)
Age, mean (range), y	34.6 (21-54)	34.4 (22-46)
Sex, No. (%)		
Male	8 (40)	5 (56)
Female	12 (60)	4 (44)
Race, No. (%)		
White	17 (85)	4 (44)
Black	2 (10)	4 (44)
Other	1 (5%)	1 (11)
BMI, mean (range), kg/m ²	27 (19-37)	31 (22-39)
AHI, mean (range), events/h	2.57 (0-11)	6.39 (0-19.5)
Daily individual nasal symptoms, mean (range)		
Nasal drainage	4.43 (2-6)	4.39 (3-6)
Nasal obstruction/blockage	5.00 (4-6)	4.75 (3-6)
Sneezing	4.41 (2-6)	4.07 (2-6)
Nasal itch	4.84 (3-6)	4.36 (3-6)
Daily TNSS, mean (range) ^a	18.68 (12-24)	17.57 (12-22)
NSS, mean (range) ^b	2.3 (2-3)	2.2 (2-3)
Interference with sleep, mean (range)	2.31 (2-3)	2.21 (2-3)
RQLQ-S score (average of all items), mean (range) ^c	4.74 (3.2-5.9)	4.45 (3.1-5.6)
Daily PNIF, mean (range), L/min	95.92 (55.7-160.0)	102.38 (20.7-188.6)
PNIF before/after oxymetazoline	0.85 (0.4-1.6)	0.93 (0.7-1.3)
FLI, mean (range), %	17.80 (0.6-52.0)	21.83 (8.1-35.9)
Snoring episodes, mean (range), No./h	6.23 (0-36.1)	8.55 (0-19.9)
Time snoring, mean (range), %	6.60 (0-32.5)	9.18 (0-18.9)
Snore time, mean (range), min	29.75 (0-151.9)	37.70 (0-77.8)
ESS total score, mean (range)	12.50 (2.0-23.0)	13.33 (7.0-20.0)
WPAI-AS questionnaire score, mean (range)		
Percentage of job hours missed	4.71 (0-33.3)	4.37 (0-20.0)
Job impairment	5.94 (2.0-9.0)	5.88 (3.0-9.0)
Other daily activity impairment	6.85 (3.0-9.0)	6.44 (4.0-9.0)

Abbreviations: AHI, apnea-hypopnea index; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); ESS, Epworth Sleepiness Scale; FLI, flow limitation index; MFNS, mometasone furoate nasal spray; NSS, nighttime symptom score; PNIF, peak nasal inspiratory flow; RQLQ-S, Rhinoconjunctivitis Quality of Life Questionnaire–Standardized; TNSS, total nasal symptom score; WPAI-AS, Work Productivity and Activities Impairment–Allergy Specific.

^a Sum of 4 individual nasal symptom scores: drainage, blockage/obstruction/congestion, sneezing, and itching.

^b The mean of the responses to 3 individual symptom scores relating to nighttime symptoms (difficulty going to sleep, nighttime awakenings, and nasal congestion on awakening) scored on a 4-point scale each morning on arising.

^c Consists of 28 items across 7 domains. Each item is scored by patients on a scale from 0 (not troubled) to 6 (extremely troubled).

Table 3. Change From Baseline in Evening and Morning Total and Individual Nasal Symptoms

Symptom	Change in symptom, mean severity		P value
	MFNS group (n = 20)	Placebo group (n = 9)	
TNSS			
Morning	−6.70	−3.00	.04
Evening	−6.90	−1.00	.01
Nasal drainage			
Morning	−1.60	−0.52	.02
Evening	−1.61	−0.13	.006
Nasal obstruction/ blockage/congestion			
Morning	−1.72	−0.71	.049
Evening	−1.53	−0.32	.03
Sneezing			
Morning	−1.72	−0.84	NS
Evening	−1.97	−0.24	.009
Nasal itching			
Morning	−1.66	−0.92	NS
Evening	−1.79	−0.32	NS

Abbreviations: MFNS, mometasone furoate nasal spray; NS, not significant; TNSS, total nasal symptom score.

mometasone furoate NS produced significantly greater improvements in morning and evening nasal drainage and nasal obstruction/blockage/congestion and evening sneezing (Table 3). Mometasone furoate NS treatment was associated with a numerically greater improvement from baseline in self-rated NSS vs placebo use (mean change, −0.77 vs −0.39; $P = .10$). From baseline to EOT, mean scores for patients in the mometasone furoate NS group decreased from 2.25 to 1.47 and in the placebo group from 2.17 to 1.78.

Nasal airflow improved significantly from baseline to the end point in the mometasone furoate NS group vs the placebo group. Mean (SD) daily PNIF increased from 95.92 (30.69) L/min to 116.40 (39.83) L/min with mometasone furoate NS therapy and from 102.38 (46.40) L/min to 105.63 (46.46) L/min with placebo use ($P = .03$) (Fig 3). Response to oxymetazoline challenge, assessed by PNIF, was unchanged after mometasone furoate NS or placebo treatment. Nocturnal upper airway resistance, indicated by FLI, was slightly improved after treatment with mometasone furoate NS but worsened with placebo use (Fig 4). Mean (SD) percentage of flow-limited breaths (FLI) decreased from 17.80% (11.41%) at baseline to 16.97% (9.82%) at EOT in the mometasone furoate NS group and increased from 21.83% (7.71%) to 29.96% (16.71%) in the placebo group ($P = .02$ for mometasone furoate NS vs placebo). No changes from treatment were seen for number of snoring episodes or percentage of time of sleep that snoring occurred.

Quality of Life

Patients receiving mometasone furoate NS experienced significantly greater improvements in QOL than did those who received placebo. Improvement in total mean RQLQ-S score from baseline with mometasone furoate NS therapy was 3 times that with placebo use (mean change of −1.8 with mometasone furoate NS vs −0.6 with placebo, $P = .03$) (Fig 5), whereas ESS, which measures sleepiness in inappropriate situations, showed a decrease from baseline with mometasone furoate NS use vs an increase with placebo use ($P < .05$) (Fig 6). Mometasone furoate NS therapy was consistently superior to placebo therapy in WPAI-AS items.

Post Hoc Analyses

Baseline data demonstrated a marginal linear correlation between job impairment and TNSS ($r = 0.57$, $P = .003$) and a weak correlation with NSS ($r = 0.38$, $P = .06$). At EOT, there was a linear correlation between change in TNSS and job impairment score in the mometasone furoate NS ($r = 0.65$, $P = .004$) and placebo ($r = 0.54$, $P = .17$) groups. A positive statistical linear correlation was also found between change in NSS and job impairment score in the mometasone furoate NS ($r = 0.6$, $P = .009$) and placebo ($r = 0.63$, $P = .09$) groups.

At baseline, weak correlations were seen for impairment of daily activity other than job/school and TNSS ($r = 0.41$, $P = .03$) and NSS ($r = 0.45$, $P = .01$). At EOT with mometasone furoate NS, change in other daily activity impairment score was significantly correlated with change in TNSS ($r = 0.62$; $P = .003$) and NSS ($r = 0.54$, $P = .01$). There were also

Table 4. Efficacy Measurements

Measurement	Mean change (from baseline to EOT)		P value
	MFNS group (n = 20)	Placebo group (n = 9)	
Mean AHI, events/h (range)	0.96	1.61	NS
NSS	−0.77	−0.39	NS
Interference with sleep	−0.68	−0.46	NS
PNIF before/after oxymetazoline	0.00	−0.04	NS
Mean snoring episodes/h (No.)	2.72	−0.32	NS
Mean percentage time snoring	3.70	1.04	NS
Mean snore time (min)	13.57	−9.09	NS
RQLQ-S score (average all items)	−1.82	−0.60	.03
WPAI-AS questionnaire			
Percentage of job hours missed	−2.19	5.82	.03
Job impairment	−1.94	−0.13	NS
Other daily activity impairment	−2.15	0.11	.03

Abbreviations: AHI, apnea-hypopnea index; EOT, end of treatment; MFNS, mometasone furoate nasal spray; NS, not significant; NSS, nighttime symptom score; PNIF, peak nasal inspiratory flow; RQLQ-S, Rhinoconjunctivitis Quality of Life Questionnaire–Standardized; WPAI-AS, Work Productivity and Activities Impairment–Allergy Specific.

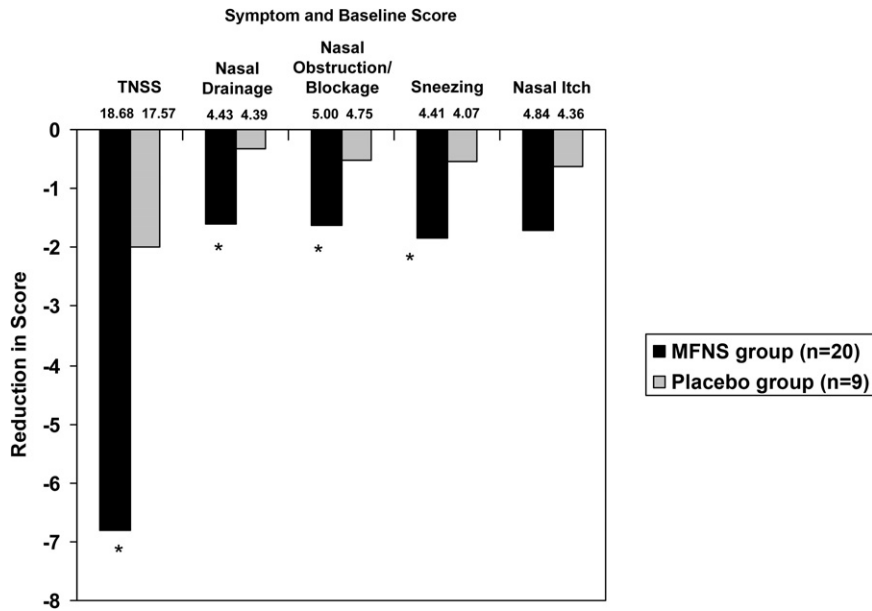


Figure 2. Improvement from baseline in mean daily total nasal symptom score (TNSS) and individual symptoms. * $P < .05$ vs placebo. MFNS indicates mometasone furoate nasal spray.

correlations between change in other daily activity impairment score and TNSS ($r = 0.57$, $P = .11$) and NSS ($r = 0.37$, $P = .34$) and placebo use. These findings indicate that the improvements in TNSS and NSS after treatment with mometasone furoate NS were significantly associated with work- and non-work-related improvements in daily functioning.

Safety Assessments

Mometasone furoate NS therapy was well tolerated, with no serious or unexpected adverse events or treatment discontinuations. Only 2 patients reported treatment-emergent adverse events: 1 ankle injury in the mometasone furoate NS group and 1 toothache in the placebo group; both were judged unlikely to be related to treatment.

DISCUSSION

In this exploratory study of 30 patients with moderate to severe PAR and RDS, subjective and objective measures of

AR, sleep quality, and daily functioning were assessed before and after 4 weeks of treatment with mometasone furoate NS or placebo. Posttreatment differences between the mometasone furoate NS and placebo groups in AHI, the primary end point, and snoring were not significant. However, significant improvements favoring mometasone furoate NS were noted for TNSS and 3 of 4 individual nasal symptom scores, objective measures of nasal airflow, sleepiness, patient-assessed QOL, and work absenteeism and daily activity level. Mometasone furoate NS therapy thus yields significant and clinically meaningful subjective and objective improvements in AR and RDS; these results suggest that improved sleep quality with mometasone furoate NS treatment does not depend on changes in airflow dynamics in the oropharyngeal regions, as reflected by AHI or snoring data.

Recent surveys indicate the frequency and impact of RDS associated with AR. In the Burden of Rhinitis in America survey,³¹ sleep adequacy scores were lower in responders

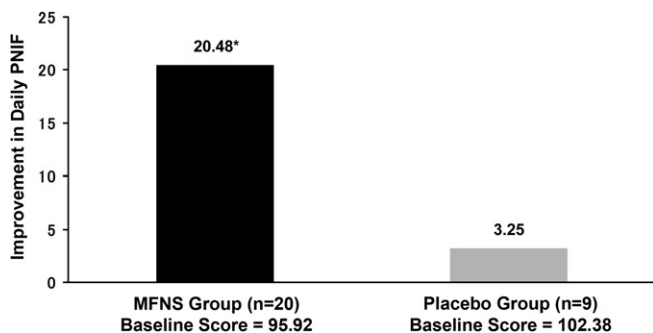


Figure 3. Improvement from baseline in mean daily peak nasal inspiratory flow (PNIF). * $P = .03$ vs placebo. MFNS indicates mometasone furoate nasal spray.

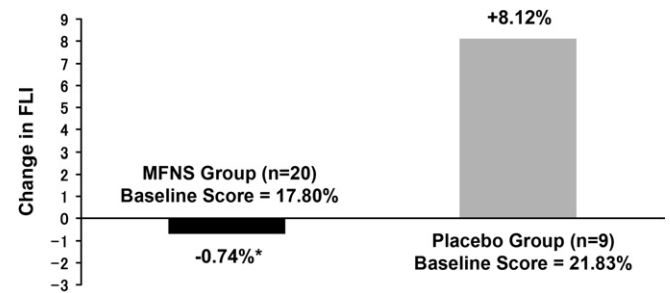


Figure 4. Mean change from baseline in flow limitation index (FLI) (expressed as percentage of flow-limited breaths). * $P = .02$ vs placebo. MFNS indicates mometasone furoate nasal spray.

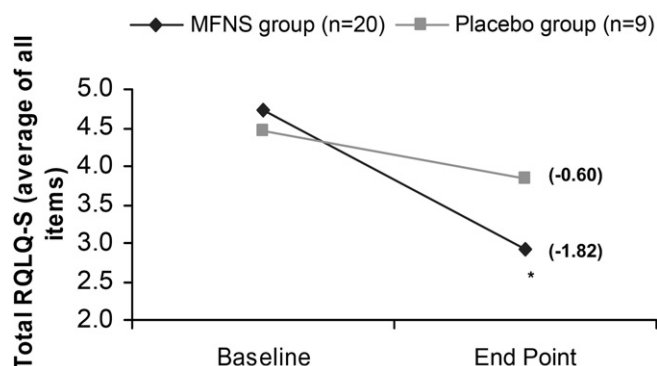


Figure 5. Mean change from baseline in total Rhinoconjunctivitis Quality of Life Questionnaire-Standardized (RQLQ-S) score. * $P = .03$. MFNS indicates mometasone furoate nasal spray.

with AR symptoms vs those without, and a direct relationship between sleep impairment and symptom severity was noted. In the Allergies in America survey,¹ 22% of adult responders with current nasal allergies reported being awakened or unable to sleep every day (12%) or most days (10%) during peak symptom periods. Congestion has consistently been shown to be the most bothersome AR symptom with the greatest effect on QOL, sleep, and daily activity.^{1,4}

SDB includes a spectrum of disorders associated with increased airway resistance during sleep ranging in severity from uncomplicated snoring to frequent episodes of apnea and hypopnea, known as OSAS.¹³ OSAS is the more common manifestation and has the greatest negative effect on sleep, daytime functioning, productivity, and QOL.^{18,32} SDB is typically diagnosed using polysomnography,³³ which records snoring, apnea and hypopnea episodes, frequency of microarousals, and other objective measures of breathing and sleep quality.³³

Pharyngeal obstruction in OSAS can occur at multiple levels³⁴ but is primarily related to partial or total collapse of the oropharynx (Fig 7).^{19,35} In contrast, airway resistance in allergic congestion occurs primarily in the nasal passages. Mechanical obstruction (with nasal packing) in healthy individuals increased the frequency of apnea and hypopnea episodes,^{36,37} and it has been suggested that increased nasal airway resistance due to AR may be a risk factor for SDB.²³ However, it is unclear whether AR-related congestion is a risk factor for SDB. Some studies^{22,38} have demonstrated more frequent apnea and hypopnea episodes in symptomatic patients with AR compared with asymptomatic patients. These differences, although statistically significant, were small (mean change in the apnea index was ≤ 1 in both studies)^{22,38} and may be clinically irrelevant. Other studies²³ found no direct correlation between congestion severity and frequency of apnea and hypopnea episodes. These data do not support a relationship between increased nasal resistance and frequency of airway collapse, suggesting that OSAS and what this article terms RDS are distinct conditions with separate etiologies (oropharyngeal mechanical obstruction in OSAS vs

nasal mucosal inflammation in RDS). Therefore, intranasal corticosteroid treatment in patients with coexisting RDS and OSAS, although improving nasal patency, sleep quality, and daily functioning, would likely have little effect on nonnasal causes of airway obstruction.

In clinical trials,²⁶⁻²⁹ mometasone furoate NS therapy has been shown to improve congestion and other nasal symptoms in patients with SAR and PAR, including those with moderate to severe disease. Significant objective improvements in nasal airflow and patency have also been demonstrated in patients with SAR and PAR.^{39,40} In patients with PAR, Naclerio et al⁴¹ found significant improvements in the RQLQ sleep domain after 2 weeks of treatment with mometasone furoate NS.

Few studies have evaluated AR treatment effects on objective changes in sleep quality, in part because polysomnography is costly and inconvenient.³³ In addition, there is poor agreement between subjective changes in sleep quality and nasal congestion and objective data obtained during monitored sleep studies.^{33,42,43} In patients with AR and a history of snoring, intranasal fluticasone propionate therapy significantly improved apnea and hypopnea frequency and congestion symptoms but left subjective sleep quality and snoring unaffected.²¹ Similar discordant effects were demonstrated in a double-blind, placebo-controlled, 8-week crossover study of fluticasone propionate use in patients with poor sleep, daytime somnolence, and congestion. Fluticasone propionate-treated patients reported greater improvements in subjective sleep quality vs placebo users ($P = .04$). However, no statistically significant differences in objective sleep outcomes (including AHI and arousals), congestion, ESS score, daytime sleepiness, restorative sleep, fatigue, or RQLQ score were noted, and there were no consistent correlations between subjective and objective sleep quality.⁴²

In the present study, mometasone furoate NS administered once daily in the morning to patients with moderate to severe PAR and RDS significantly reduced morning and evening nasal symptoms, including congestion and improved objective measures of daily nasal airflow (PNIF) and nocturnal upper airway resistance (FLI). Morning symptoms seem to be particularly problematic in patients with AR. Congestion

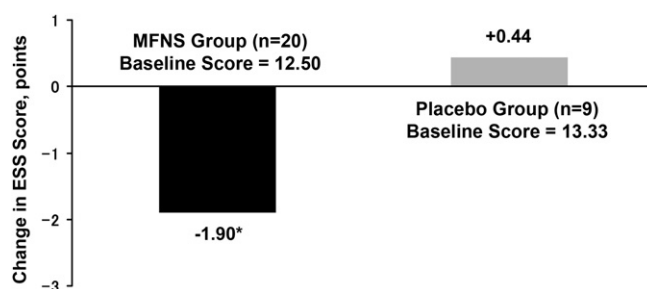


Figure 6. Mean change from baseline in Epworth Sleepiness Scale (ESS) score. * $P = .048$ vs placebo. MFNS indicates mometasone furoate nasal spray.

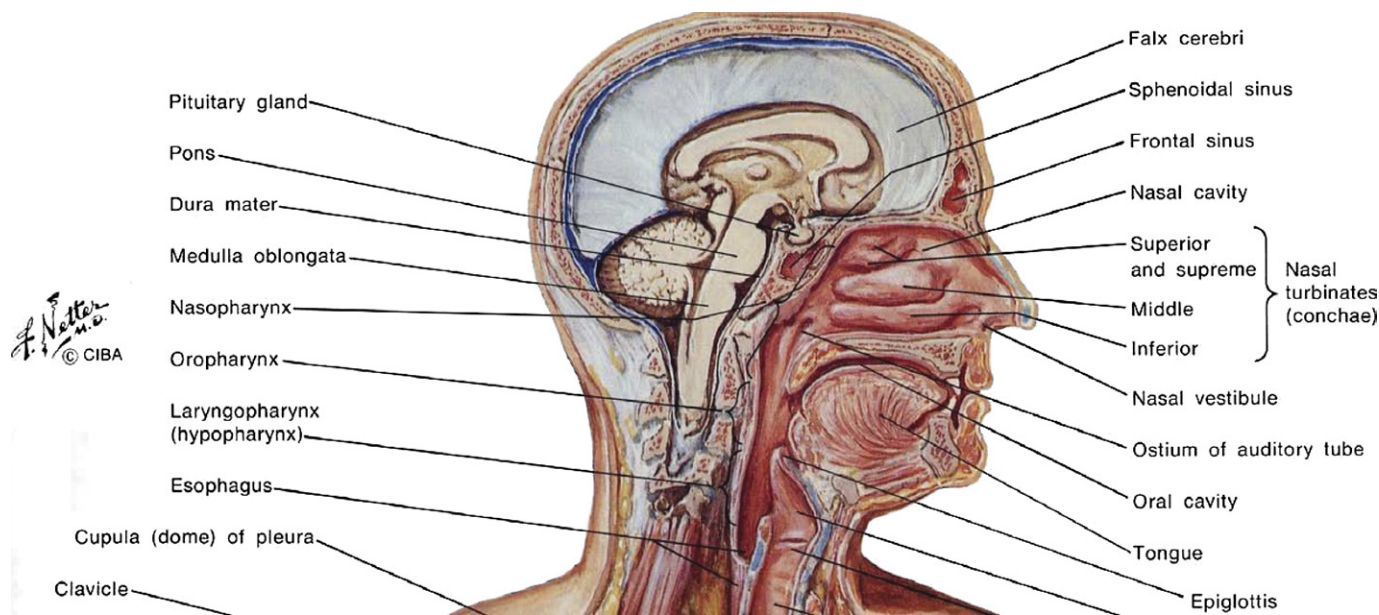


Figure 7. A sagittal section of a normal pharyngeal airway with the major variables that contribute to airway patency or collapse shown. [2009] Used with permission of Elsevier. All rights reserved.

increases in the supine position⁴⁴ and is often most severe on awakening.⁴ A recent survey⁴⁵ found that most patients with AR experience symptoms on awakening, and 24% stated that morning symptoms negatively affected the remainder of their day. Nasal congestion (reported by 85% of patients) was the most common morning symptom. Symptomatic relief on awakening and relief throughout the entire dose interval were considered important characteristics of allergy treatment by 62% and 68% of responders, respectively.⁴⁵ Sustained improvements in morning and evening nasal symptoms, including congestion, demonstrate that mometasone furoate NS therapy achieves the criteria for substantial, persistent efficacy deemed most important to patients with AR. Treatment with mometasone furoate NS did not change the before to after oxymetazoline PNIF ratio vs either placebo treatment or pretreatment values, suggesting that the decongestant effects of mometasone furoate NS are likely from reduced inflammation rather than from nasal vasculature remodeling.

Although improvements in the TNSS seen with mometasone furoate NS therapy were significant, improvements in congestion-related sleep impairment, as reflected by the NSS, did not reach statistical significance vs placebo use. However, significant improvements in subjective sleep outcomes, including daytime sleepiness as reflected by the ESS score, were observed with mometasone furoate NS treatment. Mometasone furoate NS therapy also effectively reduced QOL impairments associated with AR-related sleep disturbances, with significant improvements in RQLQ-S total score and significant increases in the amount of time patients were able to work and participate in usual daily activities. Furthermore, treatment with mometasone furoate NS reduced PAR-associated impairment in work or school performance.

Portable monitors, such as the Embletta, have been used to assess sleep disruption in patients with OSAS^{46,47}; however, this study was the first to use portable sleep monitoring to assess AR-related sleep impairment. Although polysomnography and portable sleep recorders measure apnea, hypopnea, and snoring, home sleep studies using portable devices such as the Embletta are less expensive, less time consuming, and require less patient acclimation vs polysomnography.⁴⁸ In the present study, no significant differences in the Embletta-derived outcomes, including AHI, snoring episodes, and snoring time, were observed between patients treated with mometasone furoate NS or placebo. This finding is consistent with findings by Craig et al⁴²; however, unlike results seen with fluticasone propionate therapy, the present study showed that mometasone furoate NS therapy significantly improved congestion and ESS and RQLQ scores. These results suggest that although objective sleep studies using polysomnography and portable monitors may be reliable methods for diagnosing OSAS, including sleep apnea and snoring in patients with AR, they are not sensitive tools for measuring changes in the intranasal mucosal abnormalities that compromise sleep quality in patients with AR.

Post hoc analyses demonstrated significant correlations between improvements in work and daily activity and TNSS and NSS in mometasone furoate NS-treated patients, suggesting that improvements in AR symptoms lead to better sleep and daytime functioning. These findings are consistent with a pooled analysis of data from patients with PAR treated with budesonide, flunisolide, and fluticasone propionate that showed correlations between reduction in congestion and improvement in sleep ($P < .01$) and daytime somnolence ($P = .01$).²⁵

The conclusions of this pilot study are limited by the small sample size. The finding that patients with AR and subjective sleep impairment, for which we have introduced the term RDS, report improved sleep quality after treatment with mometasone furoate NS should be confirmed in a large-scale trial. Differences in some patient baseline demographic characteristics were observed, with the placebo-treated groups showing higher values for male sex and body mass index, which are known risk factors for OSAS. At baseline, the placebo-treated arm also reported higher values for objective markers of sleep impairment, such as AHI and snoring variables. Future studies involving many patients would likely reduce these baseline between-group differences and further clarify the role of the nose and nasopharynx in AR-related sleep disturbance.

In conclusion, this is the first study, to our knowledge, demonstrating the effectiveness of mometasone furoate NS therapy in reducing nasal symptoms in patients with PAR and RDS. Mometasone furoate NS therapy also reduced absenteeism and impairment in job or school and daily activities related to PAR and RDS. The correlation between reduction in nasal symptoms, especially nasal congestion, and improved performance suggests that mometasone furoate NS therapy, through its nasal anti-inflammatory activities, can improve sleep quality, as evidenced by a reduction in daytime sleepiness. Owing to the small sample size, further investigation is warranted to determine whether these improvements translate into meaningful differences in a larger population.

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- Requests for reprints should be sent to:*
Eli O. Meltzer, MD
Allergy and Asthma Medical Group and Research Center
9610 Granite Ridge Dr, Ste B
San Diego, CA 92123
E-mail: eomeltzer@aol.com
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