

Antihistamine Use for Otitis Media with Effusion: Ongoing Opportunities for Quality Improvement

Anthony A. Prince, MD¹, Richard M. Rosenfeld, MD, MPH², and Jennifer J. Shin, MD, SM¹

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Abstract

Objectives. The otitis media with effusion (OME) clinical practice guideline endorsed by the American Academy of Otolaryngology—Head and Neck Surgery Foundation, the American Academy of Pediatrics, and the American Academy of Family Physicians recommends against using antihistamines. Avoiding antihistamines was previously endorsed as a performance measure by the National Quality Foundation, but data regarding current practice patterns are lacking. Thus, our objectives were to evaluate (1) antihistamine usage in association with OME, (2) whether practice varies according to visit setting, and (3) if usage patterns are such that a future change would be measurable.

Study Design. Cross-sectional analysis.

Setting: Ambulatory visits in the United States.

Subjects and Methods: National Ambulatory Medical Care Surveys and National Hospital Ambulatory Medical Care Surveys, 2005–2010; univariate, multivariate, and stratified analyses of antihistamine usage were performed.

Results. A total of 133,968 observations representing 1.49×10^9 pediatric visits met inclusion criteria. Antihistamines were used in 9.5% of OME visits, as opposed to 5.5% of visits without OME (univariate odds ratio, 1.83; 95% confidence interval, 1.02–3.29; $P = .042$). Multivariate analysis confirmed that OME was associated with a significant increase in nonsedating antihistamine usage (odds ratio, 3.53; 95% confidence interval, 1.62–7.71; $P = .002$), when adjusted for age, sex, race/ethnicity, allergic conditions and nasal inflammatory diagnoses.

Conclusions. Oral antihistamines are significantly more likely to be administered when OME is diagnosed. Although antihistamine use for OME is proportionally low, the high prevalence of OME creates an opportunity for quality improvement. Future changes in clinician behavior in response to an updated guideline or related performance metric could be monitored.

Keywords

otitis media with effusion, antihistamines, practice patterns, performance metric, quality improvement

A key priority in the “National Strategy for Quality Improvement in Health Care” is to make care safer by reducing harm.¹ Consistent with this priority is reducing inappropriate use of medications that are ineffective yet have associated harms, costs, and adverse events. Here, we assess opportunities for quality improvement by reducing antihistamine usage for otitis media with effusion (OME), a common condition that occurs in 50% to 90% of children.^{2–7} OME is diagnosed in 2.2 million children in the United States per annum,^{8,9} and it is the most common cause of pediatric hearing impairment in developed nations.¹⁰ Affected children may face additional challenges during speech, language, and academic development,^{11,12} as well as problems with balance and motor skills.^{13,14} OME arises in the setting of eustachian tube dysfunction, and it exists along a spectrum that may include tympanic membrane retraction, ossicular erosion, and cholesteatoma development.¹⁵ OME is a frequent reason for medical evaluation, and related costs are estimated at \$3 billion to \$5 billion per year.^{7,16–23}

The theory that allergic rhinitis is an underlying risk factor for the development of OME remains controversial.^{24,25} Antihistamines and decongestants have been proposed as treatments for children with OME because allergic rhinitis is highly prevalent and middle ear effusion has a potential allergic inflammatory component.^{25–30} Animal studies have also shown that allergen-induced nasal inflammation can result in negative middle ear pressure and impaired mucociliary clearance, factors crucial to the development of OME.^{26–28} Despite such reports suggesting a link between allergic rhinitis and OME, randomized controlled

¹Department of Otolaryngology, Harvard Medical School, Boston, Massachusetts, USA

²Department of Otolaryngology, SUNY Downstate Medical Center, Brooklyn, New York, USA

Corresponding Author:

Jennifer Shin, MD, SM, Department of Otolaryngology, Harvard Medical School, 45 Francis Street, Boston, MA 02115, USA.

Email: jennifer_shin@meei.harvard.edu

trials of antihistamine therapy show no improvement in OME outcomes.^{24,25} Systematic review and meta-analyses have demonstrated that antihistamine usage confers no clinical benefit for OME while increasing adverse effects.^{29,30} Accordingly, the multidisciplinary 2004 OME clinical practice guideline endorsed by the American Academy of Otolaryngology—Head and Neck Surgery Foundation, the American Academy of Pediatrics, and the American Academy of Family Physicians recommends against their usage, and the 2016 update is expected to do the same.⁸ Consistent with these guidelines, both the American Medical Association Physician Consortium for Performance Improvement and the American Academy of Otolaryngology—Head and Neck Surgery Foundation are considering whether actively refraining from prescribing antihistamines in OME should be a renewed performance metric for National Quality Foundation endorsement.

Given the current lack of clinical data supporting antihistamine use in OME and the associated clinical practice guidelines that recommend against their usage, our objectives were to (1) evaluate the antihistamine administration patterns in association with OME, (2) determine whether usage varies according to visit setting, and (3) ascertain if practice patterns are such that a future change might be measured.

Methods

This study utilized data from the National Ambulatory Medical Care Survey (NAMCS) and the National Hospital Ambulatory Medical Care Survey (NHAMCS). Briefly, NAMCS describes outpatient visits to office-based physicians, while NHAMCS describes visits to hospital emergency and outpatient departments. NAMCS uses a 3-stage probability sample of nonfederal, office-based physicians, and NHAMCS uses a 4-stage probability sample to represent provision of ambulatory care services in hospital emergency and outpatient departments. Application of visit weights, supplied with the survey data, generates estimates representative of all ambulatory care visits in the United States. Both surveys are conducted annually by the National Center for Health Statistics. Full descriptions of the databases are available online.^{31,32}

The planned protocol was reviewed by the Partners Institutional Review Board, which deemed the de-identified data exempt from oversight. The study population was restricted to children ≤ 18 years of age. Visits occurred between 2005 and 2010 in urgent and nonurgent settings. The primary outcome of interest was antihistamine usage (all, nonsedating, or sedating); the primary predictor variable of interest was OME. Secondary predictor variables and potential confounders included allergic rhinitis and allergic/atopic systemic conditions, as well as nasal inflammatory conditions, including upper respiratory tract infections and nonallergic rhinitis and rhinosinusitis. We defined the outcome and predictor variables, as well as potential confounding comorbidities, based on ICD-9 codes and Lexicon Plus Cerner Multum medication codes selected by the Centers for Disease Control and Prevention (Appendix

1, at www.otojournal.org/supplemental). Drugs were also coded to identify those which were newly recommended at the time of OME diagnosis, and in NAMCS/NHAMCS, prescription and nonprescription medications are tracked. For emergency room visits, medications prescribed at the time of discharge were evaluated. Basic demographic information was also tabulated, including patient age, sex, and race/ethnicity.

Analyses were planned a priori to evaluate the probability of new administration of antihistamine medication in the setting of OME, adjusted for allergic and nasal inflammatory diagnoses, as well as age, sex, and race/ethnicity. Antihistamines were categorized as nonsedating or sedating according to the Tarascon desk reference³³; antihistamines with a commercially combined decongestant were also included (Appendix 2). Topical antihistamine creams and sprays were not included, as these have not been studied in randomized controlled trials or systematic review, and were accordingly not included in the OME clinical practice guidelines.

We applied sampling weights to obtain correct standard errors based on the complex survey design. As recommended by the National Center for Health Statistics, we considered estimates based on >30 affected observations and those with a standard error of $<30\%$ of the point estimate to be reliable. Analysis of antihistamine administration for OME in the full pediatric population met these criteria. In consideration of the subset of emergency room and specialist visits, however, these criteria were not met, as fewer OME-related visits occur in these locations; thus for these visit-type analyses, the diagnostic focus was expanded to include OME, eustachian tube dysfunction, or tympanic membrane retraction (so that there would be a minimum of 30 affected observations with a standard error of $<30\%$). Univariate analysis was performed for the primary outcome and predictor variables, followed by a multivariate analysis; we utilized the survey logistic command for univariate and multivariate logistic regression models. Variables were selected for the multivariate analysis if the univariate assessment demonstrated a P value $< .2$ or if the variable was deemed to be clinically important a priori. The standard errors related to proportions were determined according to standard formulas (analytically derived variance estimator associated with the sample proportion). A post hoc analysis was also performed to evaluate the impact of the year of visit and cystic fibrosis on the results in both univariate and multivariate analyses. All analyses were performed at the 0.05 significance level through STATA 13.0 (College Station, Texas).

Results

During the study time frame, there were 133,968 observations meeting our inclusion criteria. After application of visit weights, this represents 1,491,045,375 pediatric visits. Baseline characteristics are shown in **Table 1**, and they demonstrated that children with OME were significantly younger, more likely to be evaluated by an otolaryngologist

Table 1. Baseline Demographics in Children with and without OME.

	OME Absent		OME Present		P Value
	PE	95% CI	PE	95% CI	
Mean age, y	7.3	7.2-7.4	4.2	3.6-4.8	<.05
Female, %	48.6	48.0-49.3	43.0	37.5-48.6	.05
Race/ethnicity, %					.02
Non-Hispanic white	61.9	59.3-64.6	75.4	66.7-82.4	
Non-Hispanic black	14.0	12.3-15.9	10.9	5.7-19.9	
Hispanic	18.3	15.8-21.1	9.4	6.2-14.0	
Asian	4.5	3.8-5.3	2.9	1.6-5.1	
Pacific Islander	0.3	0.2-0.4	0.01	0.01-0.04	
American Indian/Alaska Native	0.5	0.4-0.7	0.4	0.2-1.1	
Multiple races	0.5	0.4-0.6	0.7	0.1-4.4	
Visit location, %					
Emergency department	12.5	11.5-13.5	2.7	1.8-3.6	<.01
Otolaryngology subspecialist	1.6	1.4-1.9	27.8	20.5-35.0	<.01
Allergic conditions, %					
Allergic rhinitis	2.6	2.3-2.9	3.5	0.6-6.4	.46
Systemic + other A/A conditions	0.4	0.3-0.5	0.3	0.0-0.7	.60
Nasal inflammatory conditions, %					
Nonallergic rhinitis	3.5	0.3-0.4	6.8	0.3-10.7	.28
Upper respiratory tract infection	8.7	8.1-9.3	11.0	6.8-15.1	.24

Abbreviations: A/A, allergic/atopic; CI, confidence interval; OME, otitis media with effusion; PE, point estimate.

specialist, and less likely to be seen in the emergency department.

Univariate analysis demonstrated that antihistamines were newly administered significantly more often when OME was diagnosed (odds ratio [OR], 1.83; 95% confidence interval [95% CI] 1.02-3.29; $P = .042$). Antihistamines were also recommended significantly more often when allergic rhinitis was present, with a larger effect size seen (OR, 22.41; 95% CI, 17.86-28.13; $P < .001$). Antihistamines were similarly administered significantly more often when systemic atopic conditions, upper respiratory tract infection, and other rhinitis and rhinosinusitis conditions were present (univariate analysis; **Table 2**). The year in which the visit occurred was not associated with an altered odds of antihistamine administration in those with OME (OR, 1.12; 95% CI, 0.86-1.44; $P = .404$) or without OME (OR, 0.97; 95% CI, 0.92-1.02; $P = .191$).

Stratified analyses were performed to evaluate the probability of administering antihistamines with a diagnosis of OME, relative to the presence or absence of a concomitant allergic rhinitis diagnosis. Among all patients, nonsedating antihistamines were significantly more likely to be administered when OME was diagnosed (**Table 3**). This significant increase in nonsedating antihistamine usage persisted even among the subgroups in which allergic rhinitis and systemic atopy was absent. When allergic rhinitis was present, there was no difference in antihistamine administration among those with and without OME, and overall rates of antihistamine usage were significantly higher. Among those with no systemic or other allergic symptoms, usage of nonsedating

antihistamines was again significantly elevated when OME was diagnosed.

Multivariate analysis confirmed a significantly higher odds of newly administered nonsedating antihistamine therapy in the setting of an OME diagnosis (OR, 3.53; 95% CI, 1.62-7.71; $P = .002$; **Table 4**), when adjusted for age, sex, race/ethnicity, allergic rhinitis, systemic allergy and other atopy, nonallergic rhinitis, and upper respiratory tract infection. The effect size was not as great as that seen in association with allergic rhinitis or systemic atopy diagnoses (respectively, OR, 30.88; 95% CI, 23.00-41.47; $P < .001$; OR, 7.86; 95% CI, 2.73-5.56; $P < .001$). When sex and race/ethnicity were removed from the model, every variable retained the same statistical significance or nonsignificance, and the OME-related OR was similar (OR, 3.58; 95% CI, 1.65-7.76; $P = .001$). When the year of visit and diagnosis of cystic fibrosis were incorporated in a post hoc analysis, the same conclusions were reached (OME-related OR, 3.52; 95% CI, 1.61-7.71; $P = .002$).

A subsequent analysis was performed to determine whether the location of service or subspecialty care altered the probability of receiving antihistamine therapy when OME was diagnosed. Because the number of emergency room visits and subspecialists visits were fewer, when these analyses were performed, the initial verifications showed that the data specific to OME alone would not provide reliable estimates of variance; specifically, the minimum affected cell numbers were fewer than as recommended by the NAMCS/NHAMCS epidemiologic standards, and the related 95% CIs were accordingly very wide, spanning 20-

Table 2. Univariate Logistic Regression Analysis of Antihistamine Administration.

	Coefficient (SE)	OR (95% CI)	t Score	P Value
OME	0.61 (0.30)	1.83 (1.02-3.29)	2.03	.042
Allergic rhinitis	3.11 (0.12)	22.41 (17.86-28.13)	26.84	<.001
Systemic + other A/A conditions	2.56 (0.26)	12.95 (7.72-21.73)	9.70	<.001
Nonallergic rhinitis	1.14 (0.13)	3.12 (2.41-4.03)	8.71	<.001
Upper respiratory tract infection	0.43 (0.12)	1.53 (1.21-1.94)	3.48	<.001

Abbreviations: A/A, allergic/atopic; CI, confidence interval; OME, otitis media with effusion; OR, odds ratio.

Table 3. Antihistamine Administration and OME: Stratified by Allergic Rhinitis Status.

	Antihistamines					
	All		Nonsedating		Sedating	
	%	95% CI	%	95% CI	%	95% CI
All patients						
No OME	5.5	5.0-5.9	2.3	2.0-2.6	3.2	2.9-3.5
OME	9.5	5.9-15.2	4.7 ^a	2.4-9.2	4.6	2.3-9.2
New medications						
No OME	3.0	2.7-3.2	1.1	1.0-1.3	1.8	1.6-2.0
OME	5.3	3.0-9.0	3.6 ^a	1.9-6.6	1.6	0.6-4.2
New medications						
Allergic rhinitis absent						
No OME	2.1	1.9-2.3	0.6	0.5-0.8	1.3	1.2-1.5
OME	3.4	1.7-6.7	2.7 ^a	1.3-5.8	0.6	0.1-3.5
Allergic rhinitis present						
No OME	32.0	27.6-36.7	17.0	13.9-20.7	13.7	10.2-18.3
OME	54.7	34.4-73.6	26.1	10.2-52.2	28.7	12.6-52.8
Systemic + other A/A absent						
No OME	2.9	2.6-3.1	1.1	1.0-1.3	1.7	1.5-1.9
OME	5.3	3.0-9.1	3.6 ^a	1.9-6.7	1.6	0.6-4.2

Abbreviations: A/A, allergic/atopic; OME, otitis media with effusion.

^aP < .05.

fold differences. Therefore, to analyze the impact of location of service and subspecialty care, we expanded this analysis to include diagnoses of OME, eustachian tube dysfunction, or tympanic membrane retraction, to maintain sufficient numbers to support the standard survey weighting.

Here, we first investigated whether the previously observed increased probability of antihistamine administration persisted in the population with the expanded diagnostic spectrum. Again noted was an approximate doubling in the probability of treatment with antihistamines, which was statistically significant (**Table 5**). Next, visits to the emergency department were evaluated. Here, the effect was again seen and with greater magnitude: the relative risk of receiving nonsedating antihistamines was 12 times as high with OME, eustachian tube dysfunction, or tympanic membrane retraction. Among non-emergency room visits, there was also a significant elevation in antihistamine administration, although the magnitude was less than that in the

emergency department. Finally, visits to otolaryngologists were analyzed. Among these subspecialty visits, the presence of OME, eustachian tube dysfunction, or tympanic membrane retraction resulted in no elevation in administration of antihistamine therapy. Among nonotolaryngologist visits, there was a significant elevation in initiating antihistamine usage.

Multivariate analysis of the probability of receiving antihistamines in the setting of a diagnosis of OME, eustachian tube dysfunction, or tympanic membrane retraction showed that a significant increase persisted (OR, 2.12; 95% CI, 1.27-3.56; *P* = .004; **Table 6**), when the data were adjusted for age, sex, race/ethnicity, allergic rhinitis, systemic allergy and other atopy, nonallergic rhinitis, upper respiratory tract infection, and visit setting. In this analysis, the emergency department setting significantly increased the odds of receiving antihistamine therapy, while a visit to an otolaryngologist was significantly protective. When sex and race/

Table 4. Multivariate Logistic Regression Analysis of Nonsedating Antihistamine Administration and OME.

	Coefficient (SE)	OR (95% CI)	t Score	P Value
OME	1.26 (0.40)	3.53 (1.62-7.71)	3.17	.002
Age	0.02 (0.15)	1.01 (0.99-1.04)	1.57	.117
Sex	-0.02 (0.13)	0.98 (0.75-1.28)	-0.12	.901
Race or ethnicity	-0.04 (0.06)	0.96 (0.85-1.08)	-0.66	.507
Allergic rhinitis	1.28 (0.22)	30.88 (23.00-41.47)	22.82	<.001
Systemic + other A/A conditions	2.06 (0.54)	7.86 (2.73-5.56)	3.83	<.001
Nonallergic rhinitis	1.27 (0.22)	3.60 (2.32-5.56)	5.25	<.001
Upper respiratory tract infection	0.64 (0.20)	1.91 (1.28-2.82)	3.21	.001

Abbreviations: A/A, allergic/atopic; OME, otitis media with effusion.

Table 5. Antihistamine Administration and OME, Eustachian Tube Dysfunction, and Tympanic Membrane Retraction: Stratified by Location of Service and Subspecialty.

	Antihistamines					
	All		Nonsedating		Sedating	
	%	95% CI	%	95% CI	%	95% CI
All visits						
No OME	5.4	5.0-5.9	2.3	2.0-2.6	3.2	2.9-3.5
OME	10.8 ^a	7.5-15.1	5.6 ^a	3.4-9.1	5.1	3.0-8.4
ED visits						
No OME	2.8	2.6-3.1	0.3	0.2-0.4	2.6	2.3-2.8
OME	7.3	2.5-19.7	3.5 ^a	0.6-19.1	1.0	0.1-6.2
Non-ED visits						
No OME	2.9	2.7-3.2	1.1	0.1-1.3	1.7	1.5-2.0
OME	6.0 ^a	4.0-9.0	3.6 ^a	2.1-5.9	2.3	1.1-4.5
Otolaryngology visits						
No OME	2.8	2.0-3.9	1.5	0.1-2.5	1.4	0.1-2.3
OME	3.9	2.1-7.1	2.6	0.1-5.3	1.4	4.7-4.3
Nonotolaryngology visits						
No OME	2.9	2.6-3.2	1.1	0.1-1.3	1.7	1.6-2.0
OME	7.4 ^a	4.5-11.9	4.2 ^a	2.1-8.2	2.9	1.3-6.4

Abbreviations: ED, emergency department; OME, otitis media with effusion.

^a $P < .05$.

ethnicity were removed from the analysis, every variable retained the same statistical significance or nonsignificance, and the OME-related OR was nearly identical (OR, 2.14; 95% CI, 1.29-3.57; $P = .003$).

When the population with OME, eustachian tube dysfunction, or tympanic membrane retraction was restricted to those without a diagnosis of allergic rhinitis, results remained similarly significant. Among those with an OME-related diagnosis, 4.1% (95% CI, 2.5%-6.5%) received antihistamines, as opposed to 2.1% (95% CI, 1.9%-2.3%) with no OME-related diagnosis ($P < .05$). Nonsedating antihistamines were administered in 2.8% (95% CI, 1.6%-5.0%) of those with an OME-related diagnosis, as opposed to the 0.6% (95% CI, 0.5%-0.7%) baseline risk ($P < .05$). Multivariate analysis of this restricted population showed that the odds of antihistamine

administration remained approximately double (OR, 1.99; 95% CI, 1.10-3.58; $P = .023$).

Discussion

Our data suggest that there are quality improvement opportunities to enhance the care of children with OME by reducing treatment with antihistamines. Despite associated adverse events and costs, these ineffectual interventions remain in regular use for OME. Although only a minority of children were treated, the high prevalence of OME in early childhood creates a larger absolute problem of inappropriate prescribing that warrants attention and continued intervention.

We found a significant association between nonsedating antihistamine administration and OME, adjusted for age,

Table 6. Multivariate Analysis of Antihistamine Administration and OME, ETD, and TM Retraction.

	Coefficient (SE)	OR (95% CI)	t Score	P Value
OME, ETD, and TM retraction	0.75 (0.26)	2.13 (1.27, 3.56)	2.88	.004
Age	−0.01 (0.01)	0.99 (0.98, 1.01)	−1.21	.226
Sex	−0.56 (0.07)	0.95 (0.83, 1.08)	−0.82	.412
Race or ethnicity	−0.03 (0.37)	0.97 (0.90, 1.05)	−0.75	.452
Allergic rhinitis	3.19 (0.12)	24.27 (19.25, 30.61)	26.96	<.001
Nonallergic rhinitis	1.04 (0.15)	2.83 (2.09, 3.84)	6.71	<.001
Upper respiratory tract infection	0.43 (0.12)	1.53 (1.20, 1.94)	3.46	.001
Systemic + other A/A conditions	3.13 (0.21)	22.98 (15.19, 34.74)	14.87	<.001
ED visits	−0.69 (0.20)	1.35 (1.19, 1.54)	4.49	<.001
Otolaryngology visits	0.30 (0.07)	0.50 (0.34, 0.74)	−3.51	<.001

Abbreviations: A/A, allergic/atopic; CI, confidence interval; ED, emergency department; ETD, eustachian tube dysfunction; OME, otitis media with effusion; OR, odds ratio; TM, tympanic membrane.

sex, race/ethnicity, allergic conditions, nonallergic rhinitis, and upper respiratory tract infection. When the larger spectrum of OME, eustachian tube dysfunction, or tympanic membrane retraction is evaluated, the effect is statistically significant for all antihistamines and nonsedating antihistamines. Among patient visits in which allergic rhinitis was not diagnosed, the absolute risk increase for antihistamine administration was 2.0% (4.1% − 2.1% = 2.0%). Given that there are approximately 2.2 million yearly OME diagnoses, these data suggest that there are 46,200 excess antihistamine administrations in the United States per annum.

Increased antihistamine usage in association with OME, eustachian tube dysfunction, or tympanic membrane retraction is most pronounced among emergency department visits (a 10-fold increase in prescribed nonsedating antihistamines). At the time same, there are fewer OME visits to the emergency ward and a lower baseline rate of usage, so the absolute risk increase in this setting is 3.2% (nonsedating antihistamines; relative to a 2.5% increase in non-emergency department visits).

Overall, based on the most updated available national-level data available from NAMCS/NHAMCS, clinicians are significantly more likely to administer antihistamine therapy (particularly the nonsedating forms) when OME is present. Significant increases are demonstrated in univariate, multivariate, stratified, and subgroup analyses, suggesting that a potential to make a meaningful difference if withholding antihistamine therapy in the absence of concomitant allergic condition is selected as focus of clinical performance.

In addition, given that a significant measurable difference currently exists, clinician performance could be tracked over time. If this significant increase in the odds of antihistamine administration in the setting of OME dissipates after the implementation of an updated clinical practice guideline or a related performance metric, it could suggest an overall measurable change in clinician behavior in response.

While OME is associated with a significantly increased odds of antihistamine administration, the magnitude of the effect is not as high as that observed with allergic rhinitis

and systemic atopic conditions in which antihistamine therapy is appropriate. When OME is present, the odds of antihistamine administration are approximately doubled, while with allergic rhinitis and other systematic allergic conditions, the odds are elevated about 20-fold. These relative numbers also suggest that a broad-based refrainment from antihistamine usage for OME would not be cause for a radical change in national practice as a whole. Among emergency department settings, the impact may be higher, while among otolaryngologists, there may be minimal, if any, need for change.

Antihistamine usage may result in adverse effects. These may include drowsiness, fatigue, and limited concentration,³⁴ and a subset has been associated with alterations in cardiac rhythm³⁵ and anticholinergic effects.³⁶ Antihistamines directed at allergy therapy are selective antagonists of H1 receptors and may be sedating or nonsedating. Their lipophilic properties determine whether they are able to traverse the blood-brain barrier and exert central effects. Sedating antihistamines are lipophilic, while nonsedating antihistamines are hydrophilic. In the present analysis, OME was associated with significant elevations in nonsedating antihistamine use, although a statistically significant effect was not seen in sedating antihistamines. Given the anticipated decreased adverse effect profile, clinicians may have increased willingness to administer the nonsedating class of medications, resulting in a preferential increase in that group of medications.

Limitations of this study include those inherent to cross-sectional studies. Most important, cross-sectional studies cannot inherently prove a directional causal relationship. At the same time, while it may be proposed from these data that a new antihistamine administration was retroactively causative of the OME that was diagnosed at that visit, this effect is obviously less likely than the proposed reverse relationship. Another limitation of cross-sectional studies is that they are not ideal for low-incidence diagnoses; fortunately, OME is a condition with high prevalence among children. This study is also limited in that diagnoses are defined according to ICD-9 code, a process that may imperfectly

reflect the patient's true state. Such coding also does not capture the severity, duration, or nuances of disease and may be more specific than sensitive.³⁷ This database does not contain an internal metric to vet *ICD-9* diagnosis coding against another means of diagnosis, and these results are limited to a 6-year period. The database also does not directly track subsequent adverse reactions to antihistamine therapy, as the data are cross sectional. We would therefore need to rely on historical data, such as those from prior systematic reviews, which suggest a number needed to harm of 9.^{29,30} In addition, while the database tracks both prescription and nonprescription medication administration and each was continued or newly administered, it is limited in that it tracks only 8 medications per visit date. It is, however, available across this large national-level data set, which spans the gamut of ambulatory treatment sites and provider types, allowing insight into national practice patterns. These broad-spectrum data may provide more insight into national provider tendencies than that from focused inquiries of volunteer physicians or tests of methodology,³⁸ which could be subject to self-selection bias.

Conclusions

The diagnosis of OME is associated with a statistically significant increase in the administration of antihistamines. These data suggest that among the 2.2 million yearly OME diagnoses, there may be 115,800 excess antihistamine administrations per annum. The measurable difference in antihistamine prescribing patterns would allow monitoring of future changes in clinician behavior in response to an updated guideline or related performance metric.

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Author Contributions

Anthony A. Prince, drafted a portion of the initial manuscript, recorded the tabular data, and approved the final manuscript as submitted; **Richard M. Rosenfeld**, reviewed and revised the manuscript, contributed to the presentation and interpretation of the data, and approved the final manuscript as submitted; **Jennifer J. Shin**, conceptualized and designed the study, drafted a portion of the initial manuscript, reviewed and revised the manuscript, contributed to the presentation and interpretation of the data, and approved the final manuscript as submitted.

Disclosures

Competing interests: Anthony A. Prince, may begin consulting for Knopp Biosciences, LLC in the fall of 2015; Jennifer J. Shin, receives textbook royalties from *Evidence-Based Otolaryngology* (Shin JJ, Randolph GW, editors; New York: Springer, 2008) and from *Otolaryngology Prep and Practice* (Shin JJ, Cunningham MJ, editors; Plural Publishing, 2013); is a recipient of a Harvard Medical School Shore Foundation/Center for Faculty Development

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Supplemental Material

Additional supporting information may be found at <http://otojournal.org/supplemental>.

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Appendix 1 (available online only). Diagnoses

Diagnosis	Diagnosis Codes
Otitis media with effusion	381.0, 381.02, 381.03, 381.04, 381.05, 381.06, 381.10, 381.19, 381.20, 381.29, 381.30, 381.40
Eustachian tube dysfunction	381.5, 381.51, 381.52, 381.60, 381.61, 381.62, 381.63, 381.7, 381.8, 381.81, 381.89, 381.9
Tympanic membrane retraction	385.10, 385.11, 385.12, 385.13, 385.19
Allergic rhinitis	477.0, 477.1, 477.2, 477.8, 477.9
Nonallergic rhinitis and rhinosinusitis	472.0, 460.0, 784.91 461.9, 461.2, 461.1, 461.0, 461.3, 461.8, 473.4, 473.5, 473.6, 473.7, 473.9, 473.2, 473.0, 473.8, 473.3, 473.1
Systemic and other allergic conditions	995.0, 995.1, 995.3, 708.0
Upper respiratory tract infection	460.0, 465.0, 465.8 465.9

Appendix 2 (available online only). Medications

	Generic Names	Brand Names
Non-sedating Antihistamines	Desloratadine, Loratadine, Fexofenadine, Desloratadine-pseudoephedrine, loratadine-pseudoephedrine, fexofenadine-pseudoephedrine	Clarinet, Aeri, Alavert, Clear-atadine, Children's Clartin, Claritin, Allerclear, Reditabs, Fenadin, Allegra, Clarinet-D, Claritin D, Alavert D, Allegra D
Sedating Antihistamines	Clemastine, Clemastine-phenylpropanolamine, cyproheptadine, Dexchlorpheniramine, diphenhydramine, Brompheniramine-Diphenhydramine, carbinoxamine, hydroxyzine, chlorpheniramine, Cetirizine, Levocetirizine, Dimenhydrinate, triprolidine	Xyzal, Levotin, Tavist, Clemastine, Tavist D, Periactin, Polaramine, Sleep Spray, Benadryl allergy, Bena-D, Benadryl, Benahist, Benoject, Benylin syrup, Children's Benadryl Allergy Fastmelt, Siladryl, Dytuss, Dormin, Simply sleep, Q-dryl, Banophen, Dytan, Genahist, Quenalin, Di phen, Diahist Elixir, Ben-tann, Diphenadril, Diphenallin cough syrup, diphencen, Diphenhist, Diphenhydramine compound expectorant, Diphenhydramine cough syrup, Diphenhydramine Hcl Cough syrup, Diphenhydramine Hcl Elixir, Diphenhydramine Hcl expectorant, Diphenhydramine Hcl syrup, Diphenhydramine Hcl 22 GA, Sleep aid, Fenylist, Fynex, Hydramine, Hyrexin, Nordryl, Sk-diphenhydramine, Tusstat, valdrene, Wehdryl, Ednadryl, Nytol, Sleepinal, Ala Hist, Allertec, Children Zyrtec, Wal-zyr, Zyrtec, Reactin, Arabinox, Atarax, Chlor-Trimeton, Dramamine, Palgic, Karbinal ER, Tripohist