

Real-World Outpatient Prescription Patterns for Atopic Dermatitis in the United States

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Atopic dermatitis (AD) often requires combination treatment regimens. However, little is known about treatment combinations and polypharmacy in AD. We sought to characterize patterns of outpatient prescriptions and polypharmacy among US children and adults with AD. Data from the 1993–2015 National Ambulatory Medical Care Survey were analyzed, including 128,300 pediatric and 623,935 adult outpatient visits. Among AD visits, dermatologists prescribed more topical corticosteroids (TCSs, $P = 0.01$) than any other clinicians, particularly multiple TCSs ($P < 0.0001$), topical calcineurin inhibitors (TCI, $P = 0.009$), combination TCIs with TCSs ($P = 0.004$), and systemic immunosuppressants ($P = 0.003$). Prescriptions for multiple TCSs increased from ages 0 to 19 years, 20 to 39 years, and peaked at 40 to 59 years ($P = 0.0002$). Prescriptions for prednisone peaked at ages of 40 to 59 years ($P = 0.003$). A subset of AD patients was prescribed oral antibiotics (7.1%), although fewer than half had a diagnosis of bacterial infection (42.1%). The proportion of patients receiving multiple prescriptions was higher in visits to primary care practitioners versus dermatologists, those with private versus public insurance, and 50 years or older versus 20 to 49 years versus 0 to 19 years. Visits with 4 or more prescriptions by dermatologists increased between 1993–2000 (10%) and 2011–2015 (29%, $P = 0.0001$). In conclusion, significant treatment variation exists among specialists managing AD, with increasing polypharmacy over time.

Atopic dermatitis (AD) is a chronic inflammatory disease affecting 13% of children^{1,2} and 7% of adults^{3–5} in the United States. The significant burden of disease is further reflected by increased health resource utilization among AD patients, with an estimated 4,266,634 and 6,810,125 annual visits for AD and/or eczema in US children and adults, respectively.⁶ Moreover, AD patients frequently have comorbid allergic, autoimmune, cardiovascular, and neuropsychiatric disorders.^{7–9} Atopic dermatitis is a heterogeneous disorder, including variable symptoms (itch, pain, sleep disturbance, and mental health symptoms), disease course (chronic and intermittent), lesional distribution (the scalp, face, hands, feet), and severity.

The heterogeneity of AD impacts therapeutic decision making and may lead to complex real-world treatment regimen and

polypharmacy, both of which can lead to poor adherence, increased medication costs, and adverse events. In addition, topical and/or oral antibiotics are often necessary to treat skin infection in AD. However, these may also be used by some clinicians off-label to treat AD, which may be problematic in an era of growing antibiotic resistance. However, few studies have examined real-world treatment patterns and their predictors in AD patients. In this study, we sought to characterize real-world patterns and predictors of outpatient treatment regimens and polypharmacy among US children and adults with AD.

METHODS

The 1993–2015 National Ambulatory Medical Care Survey (NAMCS) is a cross-sectional national survey implemented by the National Center for Health Statistics via the Centers for Disease Control and Prevention to sample outpatient physician visits in the United States. The sampled visits are used to provide nationally representative estimates of utilization of ambulatory services throughout the United States. Participants in the NAMCS are asked to provide data on approximately 30 patient visits during a randomly assigned 1-week reporting period. Participants include nonfederally employed, office-based physicians (doctors of medicine or osteopathy) who are primarily engaged in direct patient care across an array of medical specialties. The survey uses a multistage estimation procedure using survey weights to adjust for nonresponse and reduce bias of national estimates.

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P.S. and J.S. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

P.S. and J.S. conceived and designed the study, performed analysis and interpretation of data, drafted the manuscript, critically revised the manuscript, and performed statistical analysis. J.S. obtained funding and administrative, technical, or material support and did the study supervision.

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Atopic dermatitis visits were identified by using the *International Classification of Disease, Ninth Edition*, diagnosis code 691.8. Weighted frequencies and proportions of the most common prescription therapies individually and in combination were estimated using survey weights, including topical corticosteroids (TCSs), topical calcineurin inhibitors (TCIs), topical/oral antibiotics, antihistamines, prednisone (virtually the only systemic corticosteroid prescribed), and oral immunosuppressants (methotrexate, mycophenolate mofetil, azathioprine, or cyclosporine). The results were stratified by prescriber type (dermatologist, primary care physician [PCP]) and patient characteristics, including atopic disease (yes, no), age range (0–19, 20–39, 40–59, ≥60 years), duration of visit (tertiles), and reason for visit (acute problem, routine chronic problem, flare-up of a chronic problem, nonillness care). To evaluate temporal trends and predictors of the number of prescriptions (0, 1, 2, 3, ≥4 prescriptions), data were pooled into 5-year bins to minimize variance. Polypharmacy was defined as 2 or more prescriptions for AD-related treatments and was evaluated temporally by clinician specialty (all clinicians, dermatologists, PCPs), comorbid atopic disease (no, yes), and insurance type (private, public). Rao-Scott χ^2 tests were used to examine differences of prescriptions and/or polypharmacy by clinical characteristics. All data analyses were performed using Stata (version 14.2; StataCorp LLC, College Station, TX).

RESULTS

Population Characteristics

Data were collected from a total of 128,300 pediatric and 623,935 adult visits (weighted frequency [SE]: 3,840,000,000 [371,000,000] and 16,300,000,000 [1,410,000,000]). Overall, the weighted frequencies (SE) of annual visits for AD and eczema were 984,310 (114,165) and 3,282,324 (154,566) in children and 542,367 (54,644) and 6,267,758 (110,758) in adults, respectively. This corresponds to weighted proportions (95% confidence interval) of 0.6% (0.5%–0.7%) and 1.9% (1.8%–2.1%) in children and 0.10% (0.08%–0.11%) and 0.93% (0.88%–0.98%) in adults, respectively. A large subset of patients in AD (40.6% [32.3%–49.6%]) and non-AD (46.6% [39.5%–53.9%]) visits had seen a provider 6 or more times in the past calendar year.

Common Pharmacologic Treatments of AD

The most common medications prescribed in adult and pediatric AD visits by all clinicians and particularly dermatologists and PCPs were TCSs (adults: triamcinolone and clobetasol; children: hydrocortisone) (Table 1). Prednisone was prescribed in 7.3% and 8.5% of adult AD visits to dermatologists and PCPs but was less commonly prescribed in pediatric AD visits (2.9% and 1.5%), respectively. In adults, topical tacrolimus and pimecrolimus were prescribed in approximately 1 in 20 dermatology visits for AD. Topical pimecrolimus was prescribed in approximately 1 in 10 PCP visits for AD (9.7%), whereas tacrolimus was not prescribed by PCPs (0%). In children, topical tacrolimus (8.5%) and

pimecrolimus (6.9%) were commonly prescribed in dermatology visits for AD but much less commonly prescribed in PCP visits (0.9% and 3.6%, respectively).

In adults, PCPs were numerically more likely than dermatologists to prescribe any oral antibiotics (6.3% vs 2.5%), pain medications (4.8% vs 0.6%), and anxiolytics or antidepressants (16.7% vs 4.1%). However, dermatologists were more likely to prescribe topical antibiotics (1.8% vs 0.9%) and systemic immunosuppressants (0.9% vs 0%) than PCPs but similarly prescribed any sleep medications (2.8% vs 3.3%). Similar patterns were observed in children, although prescription rates for virtually all of these medication classes were lower than those in adults, except that prescriptions for topical antibiotics were more common in children.

Drug Combinations

Among visits reporting a diagnosis of AD, dermatologists were significantly more likely to prescribe TCSs ($P = 0.01$), particularly combinations of 2 or more TCSs ($P < 0.0001$), TCIs ($P = 0.009$), combination of TCIs and TCSs ($P = 0.004$), and systemic immunosuppressants ($P = 0.003$) (Fig. 1). In particular, among patients with a diagnosis of AD but no atopic comorbidities, dermatologists were significantly more likely to prescribe TCIs ($P = 0.04$), combination of TCIs and TCSs ($P < 0.0001$), and TCSs with antihistamine ($P = 0.0001$).

Among patients with AD, those without atopic comorbidities were more frequently prescribed TCSs ($P = 0.008$), particularly 1 TCS ($P = 0.02$). On the other hand, those with asthma, food allergy, and/or allergic rhinitis were more often prescribed with antihistamines ($P < 0.0001$).

Prescriptions for a single TCS significantly decreased from ages 0 to 19 years to 40 to 59 years and remained similar at 60 years or older ($P = 0.001$). Meanwhile, prescriptions for multiple TCSs significantly increased from ages of 0 to 19 years, 20 to 39 years, and peaked at ages 40 to 59 years ($P = 0.0002$). In addition, prescriptions for prednisone peaked at ages 40 to 59 years ($P = 0.003$).

Among visits for AD and no atopic comorbidities, prescriptions of any TCI and combined TCIs with TCSs were associated with intermediate visit duration (26% and 10% in tertile 2). On the other hand, prescriptions for oral/topical antibiotics were significantly associated with the shortest visit duration (11% in tertile 1). Prescriptions for prednisone were numerically higher with the shortest visit duration ($P = 0.06$).

During AD visits classified as being for a routine chronic problem, 1 TCS was significantly less likely to be prescribed ($P = 0.003$). Antibiotics were less likely to be prescribed during AD visits classified as routine chronic problem or flare-up of a chronic problem ($P = 0.003$). Antihistamines and combined TCSs and prednisone were most commonly prescribed at AD visits classified as a flare-up of a chronic problem ($P < 0.0001$ and $P = 0.01$).

A subset of AD patients was prescribed oral antibiotics (7.1%). However, fewer than half of those prescriptions had an associated diagnosis of bacterial infection (42.1% [27.6%–58.2%]). The most

TABLE 1. Common Medications Among AD Visits

	All Clinicians (n = 619)			Dermatology (n = 384)			Primary Care (n = 108)		
	Medication	Raw Freq	Weighted Proportion (95% CI)	Medication	Raw Freq	Weighted Proportion (95% CI)	Medication	Raw Freq	Weighted Proportion (95% CI)
Adult	Any TCS	256	35.4% (30.2%–40.9%)	Any TCS	190	46.6% (40.4%–53.0%)	Any TCS	42	27.3% (19.0%–37.5%)
	Any TCI	51	8.5% (5.5%–12.8%)	Any TCI	36	9.8% (6.4%–14.8%)	Any TCI	6	9.7% (4.1%–21.3%)
	Any oral antibiotics	22	3.8% (1.4%–10.1%)	Any oral antibiotics	14	2.5% (1.3%–5.0%)	Any oral antibiotics	4	6.3% (10.9%–29.2%)
	Any topical antibiotics	12	1.5% (0.7%–2.9%)	Any topical antibiotics	8	1.8% (0.8%–4.1%)	Any topical antibiotics	2	0.9% (0.2%–3.9%)
	Any systemic immunosuppressant	3	0.5% (0.1%–0.2%)	Any systemic immunosuppressant	3	0.9% (0.3%–3.0%)	Any systemic immunosuppressant	0	0%
	Any pain medication	34	3.8% (2.3%–6.3%)	Any pain medication	1	0.6% (0.1%–3.8%)	Any pain medication	26	4.8% (2.6%–8.7%)
	Any sleep medication	29	3.1% (1.9%–5.0%)	Any sleep medication	14	2.8% (1.5%–5.1%)	Any sleep medication	6	3.3% (1.1%–9.3%)
	Anxiety or depression medication	33	8.4% (5.0%–13.8%)	Anxiety or depression medication	10	4.1% (1.5%–10.8%)	Anxiety or depression medication	17	16.7% (8.9%–28.8%)
	Triamcinolone	67	9.1% (6.2%–13.1%)	Clobetasol	54	13.1% (9.1%–18.3%)	Triamcinolone	13	10.4% (5.3%–19.3%)
	Clobetasol	67	8.5% (6.0%–12.0%)	Triamcinolone	45	10.0% (6.3%–15.4%)	Pimecrolimus	6	9.7% (4.1%–21.3%)
	Prednisone	39	7.1% (3.8%–13.0%)	Hydroxyzine	38	9.5% (6.2%–14.1%)	Prednisone	6	8.5% (2.2%–27.6%)
	Hydroxyzine	48	6.9% (4.8%–9.8%)	Hydrocortisone	29	8.2% (5.1%–13.0%)	Loratadine	6	6.4% (2.7%–14.4%)
	Hydrocortisone	41	6.3% (4.2%–9.5%)	Prednisone	22	7.3% (3.9%–13.1%)	Diphenhydramine	7	6.1% (2.8%–12.9%)
	Betamethasone	33	5.8% (3.8%–8.6%)	Fluocinonide	25	7.3% (4.5%–11.5%)	Hydrocortisone	9	5.8% (2.6%–12.7%)
	Pimecrolimus	25	5.7% (3.2%–9.9%)	Tacrolimus	23	5.7% (3.3%–9.5%)	Betamethasone	7	5.6% (2.5%–12.1%)
	Cetirizine	27	5.6% (3.3%–9.6%)	Desonide	24	5.6% (3.4%–9.2%)	Cetirizine	3	5.2% (1.6%–15.6%)
Pediatric	Fluocinonide	31	4.7% (2.8%–7.5%)	Betamethasone	20	5.2% (2.7%–10.0%)	Clobetasol	7	4.6% (1.6%–12.1%)
	Loratadine	21	3.8% (2.2%–6.5%)	Pimecrolimus	15	4.7% (2.5%–8.7%)	Hydroxyzine	4	4.1% (1.2%–12.8%)
	All Clinicians (n = 921)			Dermatology (n = 250)			Primary Care (n = 455)		
	Medication	Raw Freq	Weighted Proportion (95% CI)	Medication	Raw Freq	Weighted Proportion (95% CI)	Medication	Raw Freq	Weighted Proportion (95% CI)
	Any TCS	377	40.4% (35.2%–45.8%)	Any TCS	126	50.2% (43.7%–56.7%)	Any TCS	182	41.8% (35.2%–48.7%)
	Any TCI	81	8.9% (5.8%–13.4%)	Any TCI	40	14.7% (9.4%–22.3%)	Any TCI	21	4.5% (2.5%–8.1%)
	Any oral antibiotics	45	5.4% (3.3%–8.5%)	Any oral antibiotics	8	3.7% (1.8%–7.3%)	Any oral antibiotics	30	7.0% (4.0%–11.9%)
	Any topical antibiotics	30	2.8% (1.8%–4.6%)	Any topical antibiotics	12	4.3% (2.2%–8.3%)	Any topical antibiotics	13	2.9% (1.5%–5.6%)
	Any systemic immunosuppressant	3	0.2% (0.0%–0.9%)	Any systemic immunosuppressant	2	0.9% (0.2%–4.4%)	Any systemic immunosuppressant	0	0%
	Any pain medication	34	3.8% (2.3%–6.3%)	Any pain medication	1	0.6% (0.1%–3.8%)	Any pain medication	26	4.8% (2.6%–8.7%)
	Any sleep medication	4	0.6% (0.1%–2.3%)	Any sleep medication	1	0.6% (0.1%–3.8%)	Any sleep medication	1	0.1% (0.0%–0.6%)
	Anxiety or depression medication	8	1.0% (0.4%–2.7%)	Anxiety or depression medication	4	1.6% (0.4%–5.5%)	Anxiety or depression medication	2	0.6% (0.1%–3.0%)
	Hydrocortisone	179	19.5% (15.9%–23.7%)	Hydrocortisone	37	15.9% (11.1%–22.4%)	Hydrocortisone	112	24.1% (19.0%–30.0%)
	Hydroxyzine	81	7.6 (5.4%–10.5%)	Hydroxyzine	38	12.6% (8.4%–18.6%)	Mometasone	25	8.3% (4.8%–13.8%)
	Mometasone	45	7.3% (4.8%–10.9%)	Desonide	29	10.1% (6.5%–15.2%)	Albuterol	32	5.3% (3.1%–9.0%)

Cetirizine	82	7.2% (5.0%–10.2%)	Tacrolimus	23	8.5% (4.6%–15.2%)	Triamcinolone	31	5.2% (3.3%–8.2%)
Albuterol	75	6.7% (4.6%–9.9%)	Pimecrolimus	19	6.9% (3.8%–12.1%)	Hydroxyzine	23	5.0% (2.8%–8.8%)
Pimecrolimus	44	5.7% (3.1%–10.3%)	Triamcinolone	15	5.0% (2.5%–9.6%)	Cetirizine	22	4.3% (2.3%–7.8%)
Triamcinolone	59	4.8% (3.2%–6.9%)	Mometasone	12	4.6% (2.5%–8.2%)	Pimecrolimus	16	3.6% (1.8%–6.9%)
Desonide	55	4.6% (3.0%–6.8%)	Fluticasone	10	4.1% (2.1%–8.0%)	Amoxicillin	15	3.1% (1.3%–7.3%)
Loratadine	26	3.6% (1.8%–6.9%)	Cetirizine	11	3.2% (1.5%–6.5%)	Loratadine	9	2.8% (1.1%–7.2%)
Tacrolimus	40	3.3% (1.9%–5.6%)	Loratadine	3	1.7% (0.6%–4.7%)	Desonide	9	2.7% (1.2%–5.8%)

CI indicates confidence interval.

common antibiotics prescribed for AD were cephalixin (3.1% [1.7%–5.5%]), mupirocin (2.3% [1.5%–3.5%]), and amoxicillin (1.4% [0.7%–3.1%]).

Polypharmacy for AD

Among AD patients, the proportion of patients receiving 2 or more prescriptions was higher in visits to PCPs versus dermatologists, those with private versus public insurance, and 50 years or older versus 20 to 49 years versus 0 to 19 years, but similar between those with versus without atopic comorbidities.

There was a significant increase in the number of prescriptions over time by all clinicians and in particular dermatologists between 1993–2000 (13% and 10%) and 2011–2015 (28% and 29%, $P = 0.02$ and 0.0001). There were no significant differences in the number of prescriptions over time among PCPs ($P = 0.12$), public insurance ($P = 0.69$), private insurance ($P = 0.34$), ages 0 to 19 years ($P = 0.18$), ages 20 to 49 years ($P = 0.07$), or 50 years or older ($P = 0.21$).

DISCUSSION

This study found considerable treatment heterogeneity and polypharmacy in both children and adults with AD, which seems to be increasing over time. Polypharmacy has been associated with substantially increased health care costs, decreased adherence to treatment, increased burden from treatment, adverse effects, drug interactions, and excess health care visits.^{10–12} Polypharmacy is common among elderly patients with multimorbidity.^{10–12} However, we found that polypharmacy was common even in children and young adults with AD; however, polypharmacy was highest in AD patients older than 50 years. Polypharmacy may result from the heterogeneity of AD, including variable disease course, lesional distribution and severity, and symptoms. Atopic dermatitis patients may have a chronic course and/or intermittent flares, which warrant both maintenance and acute treatment approaches.¹³ Atopic dermatitis patients may have lesions on virtually any body site, including the scalp, face, genitals, and hands,^{14,15} which may require different TCS potencies and vehicles. Many AD patients experience sleep disturbances, for which sedating antihistamines are commonly prescribed, as well as depression, anxiety,^{16–18} and pain^{19,20} requiring medications. All of these nuances likely contribute to polypharmacy in AD patients of all ages. Atopic dermatitis patients would likely benefit from simplification of treatment regimen, use of fewer treatments, and deprescribing treatments that are redundant, ineffective, or potentially harmful.²¹ Development of more therapies with optimal efficacy and safety may simplify treatment and improve adherence and AD control.

There were considerable differences in treatment patterns for AD by patient age, provider, and encounter type. Adults with AD were more commonly prescribed prednisone, systemic immunosuppressants, and combinations of multiple TCSs compared with children with AD. These differences may reflect more severe disease

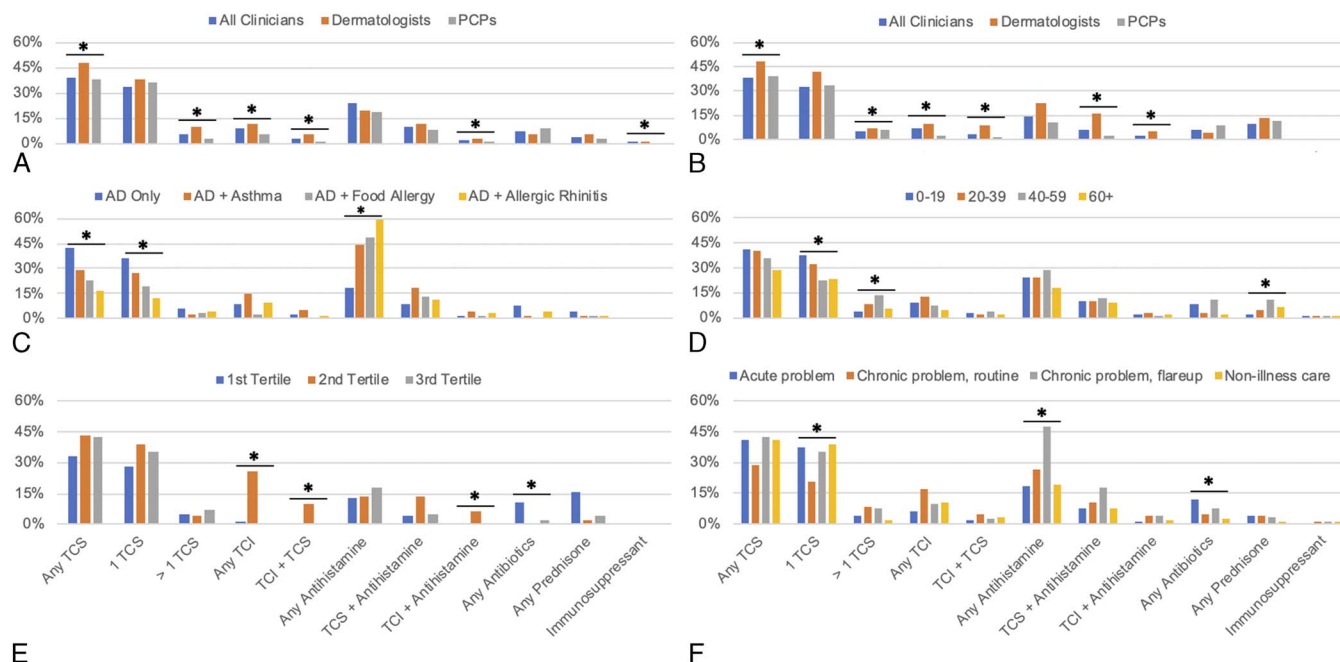


Figure 1. Drug combinations by AD visit characteristics. Each panel displays proportions of AD visits with several drug combinations involving TCSs, TCIs, antihistamines, topical/oral antibiotics, prednisone, and immunosuppressants versus clinician and patient characteristics. Panels represent AD with or without atopic comorbidity stratified by specialty (A), AD without atopic comorbidity stratified by specialty (B), AD with versus without atopic comorbidity (C), AD with or without atopic comorbidity stratified by age (D), AD without atopic comorbidity stratified by visit duration (E), and AD with or without atopic comorbidity stratified by major reason for visit (F). Rao-Scott χ^2 tests were conducted between each drug combination and visit characteristic, with asterisks denoting statistical significance.

among adults using health care for AD in the United States. Previous studies found that the US prevalence of AD decreases with age throughout childhood and remains stable throughout adulthood.^{1-3,5,22} However, the proportion of moderate to severe AD increases with age throughout childhood and into adulthood.^{1-3,5,22} We previously found that the frequency of outpatient visits peaks during infancy and decreases with age in the United States.⁶ Moreover, we found that US adults with AD have fairly low rates of outpatient health care utilization for their AD, with disease severity being the strongest predictor of utilization.²³ Together, it seems that fewer adults in the United States seek outpatient care for their AD, but those who do tend to have more severe disease that requires polypharmacy and more aggressive treatment approaches. Alternatively, it may be that treatments, such as prednisone and systemic immunosuppressants, are not as commonly prescribed in children because of greater concern for their toxicity. Of note, there were no significant differences of treatment patterns and polypharmacy between AD patients with public or private insurance. Thus, it seems that the issues identified in this study are system-wide and not related to disparities.

Topical corticosteroids were the most commonly prescribed treatment in AD patients, which is consistent with a previous study from the NAMCS between 1990 and 2000.²⁴ In addition, TCSs and TCIs were similarly prescribed by dermatologists in adults and children, although TCIs were prescribed much less commonly than TCSs. This pattern may reflect physician and/or patient concerns

about the black box warning assigned to TCIs by the US Food and Drug Administration. Alternatively, dermatologists may not routinely address long-term treatment goals and/or consider steroid-sparing agents. Topical calcineurin inhibitors were rarely prescribed by PCPs. PCPs may benefit from improved education about the use of nonsteroidal treatments in AD. Dermatologists were more likely to prescribe higher-potency TCSs, combinations of multiple TCSs and TCIs, and/or antihistamines. Although tailoring TCSs and combination therapy is part of the art and science of dermatology, it can be confusing for patients and lead to polypharmacy and its harmful consequences.

Antihistamines and prednisone were commonly prescribed in AD patients, particularly for flare-ups of chronic AD. Furthermore, oral antibiotics were prescribed for many AD patients without any diagnosis of an infection. These treatment patterns may not be consistent with the current AD treatment guidelines.^{13,25,26} Oral antihistamines are ineffective and not recommended for treating itch and cutaneous inflammation in AD; only sedating antihistamines are recommended for consideration in AD patients with sleep disturbances or atopic comorbidities.^{13,26} Some antihistamine prescriptions may have been for sleep disturbances and atopic comorbidities. However, high rates of antihistamine use were found even in AD patients without a diagnosis of atopic comorbidities. Sleep disturbances were not coded in any AD patients, which precluded our examination of antihistamine use for sleep disturbances. Systemic corticosteroids are not recommended in most

treatment guidelines because of their poor adverse event profile and inadequacy for long-term management of chronic AD patients.^{13,26,27} Finally, topical and oral antibiotics are recommended only for treatment of skin infections in AD patients and not for AD per se.^{13,25,26} Unnecessary use of antibiotics is particularly concerning in an era of growing global antibiotic resistance. Clinicians should consider these evidence-based guidelines in therapeutic decision making.

Atopic dermatitis visits with prescriptions for oral antibiotics and prednisone were associated with shortest visit duration. Furthermore, there were no differences of visit duration among AD patients prescribed combination therapies or systemic immunosuppressants. Patients prescribed combination therapy warrant more education about how to use their complex regimen. Moreover, patients prescribed systemic treatments are more severe and warrant intensive education about their disease, trigger avoidance, emollient use, and the risks and benefits of systemic therapy. Patients prescribed combination and systemic treatment warrant longer visits and additional strategies aimed at improving patient education.

The major strength of this study is the use of the NAMCS, which remains the only source of nationally representative data on outpatient physician office visits. Potential limitations include sampling on patient visits and not individual patients, preventing analysis of the longitudinal disease course in individual patients. Identification of AD and its comorbidities is limited by accurate coding. Finally, data on the severity and course of AD and comorbidities were not assessed. Future studies are needed to address the impact of these factors on prescribing patterns.

Complex therapeutic regimen, polypharmacy, and non-evidence-based treatments are commonly used in AD patients in the United States. Consideration of the complexity of and evidence-based guidelines for the pharmacologic management of AD is paramount to improving treatment adherence and effectiveness, as well as patient safety.

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