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A Multi Year Cross Sectional Study of US National Prescribing Patterns of First Generation Sedating Antihistamines in Older Adults with Skin Disease

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Abstract

Background: First generation antihistamines (FGA) medications are classified as “potentially inappropriate” for use in older adults. However, the prevalence and factors associated with their use have not been studied.

Objective: To examine FGA prescriptions in older adults who visit dermatology offices, and compare them to those of younger adults, and to those who visit primary care physicians (PCP).

Methods: This is a multi-year cross-sectional observational study including data from the United States National Ambulatory Medical Care Survey (2006–2015), collected from the physicians on a sample of patient visits to non-federally employed office-based physicians. Visits by patients aged 18 or older were included in the study: 15,243 dermatology office visits, and 66,036 PCP visits.The main outcome was FGA precription. Other variables measured included physician specialty (dermatologist or PCP), patient’s age, diagnosis of dermatological conditions, and reason for visit.

Results: FGA prescription rates were similar for adults 18–65 years and older adults (1.2% vs. 1.5%, p-value=0.19). FGA prescription rates did not differ by age even when the visit diagnosis was dermatitis or pruritus (4.8% vs. 3.7%, p-value=0.21) or when the itch was a complaint (6.7%

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Conflict of Interest:
None.

vs. 7.6%, p-value=0.64). FGA prescription rates among dermatology visits was lower than among PCP visits in analyses matched for patient and visit characteristics (3.9% vs. 7.4%, p-value=0.02).

Conclusions: Our finding that FGA prescription rates do not differ by age suggests potential overuse of FGA in older adults. Our findings also suggest that dermatologists are less likely to prescribe FGA compared to PCP in similar clinical circumstances.

INTRODUCTION

By 2030, one in five Americans will be older than 65 years, with the fastest growing segment of the US population – those over 85 years – expected to double from 4.7 million in 2003 to 9.6 million in 2030[1]. As the number of older adults continues to increase, there is an urgent need to incorporate principles of geriatrics into the clinical practice of dermatology[1].

First generation antihistamines (FGA) are used to treat skin diseases, including chronic pruritus. This is particularly relevant since the symptom of chronic pruritus or itch is especially common among older adults and accounts for almost 7 million physician visits each year[2]. However, the vast majority of itch experienced by older adults is not histamine-mediated[3], making the benefit of these prescriptions questionable.

Safe prescribing of medications has been identified by the American Geriatrics Society (AGS) as a priority. First generation antihistamines are synthesized from similar chemical stems as anticholinergic agents, leading to receptor non-specificity and anticholinergic side effects. In addition, these compounds are able to cross the blood brain barrier, leading to effects on sleep/wake cycle, memory, and concentration[4]. Anticholinergic medications pose substantial risks to older adults, including cognitive impairment, falls, and side effects such as confusion, dry mouth, and constipation.[5–10] Based on this evidence, FGA are classified as “potentially inappropriate” for use in older patients: the AGS recommends providers “avoid” them and lists the strength of that recommendation as “strong” due to their significant anticholinergic effects[5].

In this study, we examine first generation antihistamine prescriptions in older adults with skin disease, and compare the prescription rates to those of younger adults. We hypothesized that certain subgroups, such as oldest patients, would receive fewer first generation antihistamines, given the increased risks of adverse effects in older patients. Additionally, we examine the differences in prescription patterns between dermatologists and primary care physicians (PCPs). We hypothesized that dermatologists are more aware of risks of antihistamines, and their lack of efficacy in most forms of chronic pruritus, and would therefore be less likely to prescribe them.

METHODS

Data source

The National Ambulatory Medical Care Survey (NAMCS) is a national survey designed to collect information about the use of ambulatory medical care services in the United States[11]. Information is collected from the physicians on a sample of patient visits to non-federally employed office-based physicians. Each participating physician is assigned to a 1-week

reporting period, during which information on visits is abstracted using Patient Record form[12]. Data obtained during the visit includes patient demographics, patient's reason for the visit (including symptoms), physician's diagnoses, services ordered or provided, and treatments (including medications). Additionally, basic information about the physician and his or her practice is collected.

We analyzed the NAMCS datasets from 2006 to 2015. During the study period, between 1,300 and 3,800 physicians participated every year, with average response rate of 50.2%[13]. We limited our analyses to visits by patients age 18 or older because dermatological symptoms in younger patients might be caused by different mechanisms and can be treated differently. Additionally, we only considered the visits in two subspecialties: dermatology and primary care. This resulted in a sample of 81,279 visits: 15,243 visits to a dermatology office, and 66,036 visits to a primary care provider.

Measures

For each visit we identified whether the visit resulted in a prescription (new or continued) of first generation antihistamines, as recorded by the abstractor using the question, "Were any prescriptions or non-prescription drugs ORDERED or PROVIDED (by any route of administration) at this visit?". The number of possible medications reported ranged from 8 in 2006 to 30 in 2015. The list of medications used to identify ingredients in first generation antihistamines is reported in Table 1. We also collected information on multicomorbidity, defined as presence of two or more of the following conditions: arthritis, cancer, cerebrovascular disease, chronic obstructive pulmonary disease, congestive heart failure, depression, diabetes, and hypertension. The presence of any one of the above conditions was assessed using the following question on the Patient Report form: "Regardless of the diagnoses previously entered, does the patient now have –", and a list of potential conditions. Polypharmacy was defined as prescription of 6 or more medications at the visit[14]. Diagnoses related to the visit were recorded using the question, "As specifically as possible, list diagnoses related to this visit including chronic conditions". Diagnosis of dermatitis was identified by ICD9 codes 691.xx, 692.xx, 693.xx, and 708.0, and diagnosis of pruritus (itch) was identified by ICD9 code 698.xx. The symptom of itch was identified using the question, "List the first 5 reasons for visit (i.e., symptoms, problems, issues, concerns of the patient) in order in which they appear. Start with the chief complaint and then move to the patient history for additional reasons." Report of itch at any of the 5 fields was included in the analysis. For each visit, we determined whether the payment was covered by private insurance or one of the following non-private sources: Medicare, Medicaid or CHIP or other state-based program, self-pay, or other source.

Analysis

First, we described the characteristics of older patients (≥65 years old) visiting a dermatologist, and compared those patients who did and did not receive FGA prescriptions at their dermatology visits. The goal was to identify possible factors associated with FGA prescription in older adults. Factors considered were age (65–74, ≥75), gender, race (white vs. non-white), insurance type (private vs. non-private), reason for the office visit (chronic vs. non-chronic problem), presence of 2 or more chronic conditions, polypharmacy,

dermatitis or pruritus diagnosis, and itch symptom[15]. Following the univariate analyses, we performed multivariate logistic regression to assess if any of the risk factors identified in the unadjusted analyses remained associated in adjusted analysis. The regression model included all the variables described above. Observations with missing values for insurance type (n=222) or reason for visit (n=109) were excluded from multivariate analysis.

Next, we compared the prescription rates between younger and older dermatology patients, overall and in two subgroups: those with dermatitis or pruritus diagnosis, and those with an itch symptoms. The differences were assessed using chi square tests.

Finally, we compared the rates of antihistamine prescriptions in older adults (age≥65) between primary care providers and dermatologists. First, we compared the prescription rates of FGA among all PCP and dermatology visits by older adults in two subgroups: patients with a dermatitis or pruritus diagnosis, and patients who presented a symptom of itch. Next, since PCP and dermatologists see patients with different medical conditions, we limited the sample of PCP visits to only those visits with at least one of the 50 most common dermatologic diagnoses[16]. In order to further account for any possible differences between demographic or health factors between patients visiting a dermatology office and PCP office, we matched the patients with common dermatological diagnoses using Propensity Score Matching (PSM)[17]. In the matching process we accounted for the following variables: age (65–74, ≥75), gender, race (white or not white), type of insurance (private or not private), reason for the office visit (chronic vs. non-chronic problem), multicomorbidity, polypharmacy, and whether the visit took place before or after 2012 (the year Beers Criteria for Potentially Inappropriate Medication Use in Older Adults was published). Propensity score matching identifies pairs of patients, one with dermatology visit and one with PCP visit, who have similar probability of being dermatology patients given the variables above. The antihistamine prescription rates in the two matched groups were then compared using McNemar's test.

We report the unweighted raw number of surveys completed, and the weighted percentages those surveys represent after adjusting for survey weights and design factors. Statistical analyses were performed using SAS 9.4[18] and StataMP 14[19].

RESULTS

Over the 10-year study period, we identified 15,243 visits to dermatologists, 5,967 (39%) of which were by patients 65 years old or older (Table 2). Among dermatology patients older than 65 years, 50% were women, the majority were white (93%) and 82% had a non-private insurance. The most common diagnoses coded by physicians were actinic keratosis, malignant neoplasm of skin, other seborrheic keratosis, contact dermatitis and other eczema, and personal history of malignant neoplasm of skin. Overall, 14% of visits had a diagnosis of pruritus or dermatitis. The most common reasons (symptoms) for the visit reported by patients were skin lesion, discoloration or abnormal pigmentation, skin cancer and skin rash. The symptom of itch was reported by patients as a reason for the visit in 5% of visits. First generation antihistamines were prescribed in 1.5% of visits to dermatologists among adults over 65 years.

Older dermatology patients with FGA prescriptions were more likely to be diagnosed with dermatitis or pruritus (34% vs. 13%, p-value<0.001), more likely to report itch as the reason for visit (27% vs. 5%, p-value<0.001), less likely to be white (87% vs. 93%, p-value=0.04), more likely to have a chronic problem (56% vs. 42%, p-value=0.05), and more likely to have 6 or more prescriptions at the visit (40% vs. 12%, p-value<0.001) compared to older dermatology patients without FGA prescription. Age, gender, insurance type, and multicomorbidity were not associated with prescription of first generation antihistamines in older adults during dermatology visits (Table 2). In analyses adjusted for the demographics, health, and visit characteristics, we found evidence that polypharmacy (AOR=4.7; 95% CI 2.2–10.1), diagnosis of dermatitis or pruritus (AOR=2.2; 95% CI 1.2–3.9), and itch as the reason for visit (AOR=4.7; 95% CI 2.1–10.9) remained associated with first generation antihistamines prescription (Table 2).

Among 15,243 visits to dermatology, first generation antihistamine prescription rates were similar for adults 18–65 years and older adults ≥65 years. Specifically, there were no significant differences in FGA prescription rates overall (1.2% visits by patients age 18–65 vs. 1.5% visits by patients age ≥65, p-value = 0.19). Furthermore, there were no significant differences in FGA prescription rates among visits with a diagnosis of dermatitis or pruritus (4.8% visits by patients age 18–65 vs. 3.7% visits by patients age ≥65, p-value=0.21) or among visits during which itch was the reported as a reason for the visit (6.7% visits by patients age 18–65 vs. 7.6% visits by patients age ≥65, p-value=0.64) (Table 3).

Of 66,036 visits to PCP, 16,995 (25.7%) were by patients 65 years old or older. Overall, the prescription rate of first generation antihistamine among older patients in PCP office was 4.5%. Patients with diagnosis of dermatitis or pruritus were more likely to be prescribed first generation antihistamine in PCP office than those with other diagnoses (14.3% vs. 4.3%, p-value<0.001). Similarly, patients who reported itch as the reason for the visit were more likely to receive first generation antihistamine prescription than those who did not (14.7% vs. 4.4%, p-value<0.001) (Table 4). In comparison, 3.7% of dermatology patients with diagnosis of dermatitis or pruritus (3.7% dermatology visits vs. 14.3% PCP visits, p-value<0.001), and 7.6% of the dermatology patients with itch as the reason for the visit (7.6% dermatology visits vs. 14.7% PCP visits, p-value=0.02) were prescribed first generation antihistamines.

We identified 685 (4.0%) primary care visits in patients over 65 years who had at least one diagnosis from the 50 most common dermatologic diagnoses[16]. Among 5,967 visits to dermatology visits, 4,206 (70.5%) had one of such dermatology diagnoses. Using propensity score matching we matched 637 (93.0%) dermatology and PCP visits. The rate of first generation antihistamines prescriptions at dermatology visits in the matched sample was lower than the rate at PCP visits (3.9% dermatology visits vs. 7.4% PCP visits, p-value=0.02).

DISCUSSION

Patients older than 65 years received first generation antihistamine prescriptions at approximately 1.5% of dermatology visits, a prescription rate similar to that among younger

patients. Patients were more likely to receive a FGA if their presenting symptom was itch, or if their diagnosis was dermatitis or pruritus. Dermatologists were less likely than primary care doctors to prescribe a FGA to patients with itch or dermatitis. More specifically, comparison of PCP and dermatology visits similar in patient and visit characteristics suggests that dermatologists were less likely to prescribe first generation antihistamines compared to primary care physicians in similar clinical circumstances.

Our finding that first generation antihistamine prescription rates do not differ by age, suggests potential overuse of FGA in older adults with skin disease. Our findings also show that dermatologists and primary care providers differ in their use of first generation antihistamine in older patients with skin disease.

Many first generation antihistamines are considered ‘Potentially Inappropriate Medications’ in older adults by the AGS Beers Criteria[5] because of the potential for adverse effects in this patient population. In addition to well-documented adverse effects associated with central nervous system, a large systematic review has recently shown that FGA use is associated with increased risk of injurious falls and fractures in elderly adults[20]. Although we hypothesized that older patients would have lower rates of FGA prescriptions, we did not find this to be the case. This is despite the fact that most chronic pruritus is mediated by non-histaminergic pathways that are not targeted by first generation antihistamines[3]. Many older patients with skin disease may therefore be put at risk of adverse events from first generation antihistamine without evidence that these medications would provide therapeutic benefit.[21]

To put the prescription rate of first-generation antihistamines in perspective, in the year 2015 it is estimated that at least 433,480 dermatology visits by older adults were associated with a FGA prescription. It is certainly likely that some of these were appropriate and therapeutically useful prescriptions, with provider and patient balancing risk and benefit. However, we did not find a statistically significant difference in first generation antihistamines prescriptions between older and younger patients, which would be expected if physicians took the risk of FGA to older patients into account. It appears that dermatologists may not be tailoring their prescription patterns of FGA to the unique needs of older adults. This finding is consistent with prior studies showing that patient characteristics are not always taken into account when caring for older adults with skin disease. For example, a patient’s life expectancy does not affect the choice of treatment of skin cancer in the United States [22].

We expected to see differences in FGA prescriptions by gender, because men are more likely to suffer from urinary side effects due to antihistamines. Similarly, patients with compromised health are most susceptible to adverse effects of any medication[23], and we expected to see a lower rate of first generation antihistamines among patients with higher number of comorbidities. However, we found no statistically significant differences in FGA prescriptions by gender or medical comorbidities.

Primary care physicians treating older patients with common dermatological conditions prescribed first generation antihistamines in 7.4% of visits. This is consistent with previous work in NAMCS showing a “high-risk anticholinergic prescription” (including, but not

limited to, antihistamines) was prescribed in 6.2% of office visits for adults 65 and older.[15] In comparison, dermatologists prescribed first generation antihistamines in 3.9% of the visits with common dermatological diagnoses and similar patient characteristics. The difference in FGA prescription rate between dermatologists and PCPs is statistically significant, however there may be clinical reasons that justify this difference. PCPs may be more familiar with their patients' medical history and overall health, and are therefore be able to better assess individual needs and the balance of risks and benefits of treatments to individual patients.

Our study has several limitations. First, the NAMCS survey is a cross sectional survey including a small portion of office visits. Nonetheless, the survey is nationally representative and the largest of its kind in the US. Second, in the early years of data collection, a maximum of 8 prescriptions were recorded, but that number increased to 30 by 2015. Third, we have diagnoses recorded by physicians at that visit, but prescriptions can be written without a diagnosis code (for example, a physician might renew an older FGA prescription). Fourth, because the dataset does not include the list of all the medications that the patient might be taking at the time of the visit, but only the medications prescribed or renewed at that specific visit, underestimation of FGA prescriptions in our study is therefore possible if patients were already taking medications prescribed by another physician. Finally, a fundamental issue with the anticholinergic side-effects in older patients is the cumulative anticholinergic burden[24] rather than the anticholinergic effect of a single individual medicine. The NAMCS methodology does not allow for a complete assessment of a patients anticholinergic burden due to multiple medications.

We hope that collaboration between dermatologists, geriatricians and primary care physicians can improve the care of older adults with skin disease. We need to simultaneously increase awareness about the risks of prescribing first generation antihistamines to older adults, while also increase knowledge about alternative safer targeted antipruritics. By applying principles of geriatrics to dermatology and principles of dermatology to primary care, we can ultimately better care for all older adults with skin disease.

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WHAT'S KNOWN/WHAT'S NEW STATEMENTS

What's already known about this topic?

First generation antihistamines (FGA) are shown to pose substantial risks to older adults, including cognitive impairment, falls, confusion, dry mouth, and constipation. Therefore FGA are classified as "potentially inappropriate" for use in older patients by American Geriatrics Society. It has also been shown that dermatologists do not always take patient characteristics (such as age or life expectancy) into account when deciding on a treatment, and instead follow "one-size-fits-all" approach.

What does this study add?

First generation antihistamines are often prescribed during dermatology visits, and prescription rates do not differ between older and younger adults. There were no significant differences in prescription rates when comparing younger and older adults with the same diagnosis or symptom, e.g. dermatitis, pruritus, or itch. FGA are prescribed at higher rates in primary care offices than in dermatology offices.

Table 1:

List of first generation antihistamines included in the study.

First Generation Antihistamines
Brompheniramine
Carbinoxamine
Chlorpheniramine
Clemastine
Cyproheptadine
Dexbrompheniramine
Dexchlorpheniramine
Dimenhydrinate
Diphenhydramine (oral)
Doxylamine
Hydroxyzine
Meclizine
Promethazine
Triprolidine
Methapyrilene
Phenindamine
Pheniramine
Phenyltoloxamine
Pyrilamine
Chlorcyclizine
Tripelennamine

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Table 2:

Characteristics of dermatology patients 65 years old or older, and adjusted odds ratios for first generation antihistamines prescription.

Characteristics	Total	No First Generation Antihistamines Prescription	First Generation Antihistamines Prescription	Unadjusted p-value	Adjusted OR	Adjusted p-value
Unweighted N	5967	5871	96			
Weighted N	121269336	119457990	1811346			
Age						
65–75	3010 (50%)	2959 (50%)	51 (53%)	0.66	1	0.28
≥75	2957 (50%)	2912 (50%)	45 (47%)		0.7 (0.4,1.3)	
Gender						
Women	2937 (50%)	2877 (50%)	60 (63%)	0.07	1	0.22
Men	3030 (50%)	2994 (50%)	36 (37%)		0.7 (0.3,1.3)	
Race and Ethnicity						
Non-white	446 (7%)	431 (7%)	15 (13%)	0.04	1	0.25
White	5521 (93%)	5440 (93%)	81 (87%)		0.6 (0.3,1.4)	
Insurance Type						
Non-Private	4710 (82%)	4634 (82%)	76 (89%)	0.10	1	0.24
Private	1035 (18%)	1017 (18%)	18 (11%)		0.7 (0.3,1.3)	
Reason for visit						
Non-Chronic problem	3334 (57%)	3284 (58%)	50 (44%)	0.05	1	0.06
Chronic problem	2524 (43%)	2479 (42%)	45 (56%)		1.8 (1,3.2)	
Number of comorbid conditions						
<2	4521 (77%)	4453 (77%)	68 (79%)	0.67	1	0.14
≥ 2	1446 (23%)	1418 (23%)	28 (21%)		0.5 (0.2,1.3)	
Number of medications						
<6	5022 (87%)	4973 (88%)	49 (60%)	<.0001	1	<0.001
≥6	945 (13%)	898 (12%)	47 (40%)		4.7 (2.2,10.1)	
Dermatitis and/or Pruritus Diagnosis[1]						
No	5118 (86%)	5058 (87%)	60 (66%)	<0.001	1	0.01

Characteristics		Total	No First Generation Antihistamines Prescription	First Generation Antihistamines Prescription	Unadjusted p-value	Adjusted OR	Adjusted p-value
Yes		849 (14%)	813 (13%)	36 (34%)		2.2 (1.2,3.9)	
Itch Symptom							
No		5710 (95%)	5633 (95%)	77 (73%)	<0.001	1	<0.001
Yes		257 (5%)	238 (5%)	19 (27%)		4.7 (2.1,10.9)	

[1] ICD9 codes for dermatitis: 691.xx, 692.xx, 693.xx, and 708.0; ICD9 code for pruritus (itch): 698.xx.

Table 3:

Comparison of first generation antihistamine prescription rated among dermatology patients younger and older than 65 years in diagnosis subgroups.

Characteristics	First Generation Antihistamines prescription rate in dermatology visits among patients 18–65	p-value	First Generation Antihistamines prescription rate in dermatology visits among patients ≥65	p-value	p-value comparing younger and older patients
Overall	135/9276 (1.2%)		96/5967 (1.5%)		0.19
Dermatitis and/or Pruritus Diagnosis					
No	66/7925 (0.6%)	<0.001	60/5118 (1.1%)	<0.001	<0.01
Yes	69/1351 (4.8%)		36/849 (3.7%)		0.21
Itch Symptom					
No	112/8960 (1.0%)	<0.001	77/5710 (1.2%)	<0.001	0.48
Yes	23/316 (6.7%)		19/257 (7.6%)		0.64

Table 4:

Comparison of first generation antihistamine prescription rated among adults 65 years old older in dermatology and primary care physician office visits.

Characteristics	First Generation Antihistamines prescription rate in dermatology visits	p-value	First Generation Antihistamines prescription rate in PCP visits	p-value	p-value comparing dermatology visits to PCP visits
Overall	96/5967 (1.5%)		791/16995 (4.5%)		
Dermatitis and/or Pruritus Diagnosis					
No	60/5118 (1.1%)	<0.001	757/16777 (4.3%)	<0.001	<0.001
Yes	36/849 (3.7%)		34/218 (14.3%)		<0.001
Itch Symptom					
No	77/5710 (1.2%)	<0.001	778/16913 (4.4%)	<0.001	<0.001
Yes	19/257 (7.6%)		13/82 (14.7%)		0.02