

# Frequency of Drug Allergy and Associated Factors Reported by Patients Applying to the Internal Medicine Outpatient Clinic

## *İç Hastalıkları Polikliniğine Başvuran Hastalar Tarafından Bildirilen İlaç Alerjisi Sıklığı ve İlişkili Faktörler*

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### Abstract

**Introduction:** We aimed to determine the frequency of drug allergy and the risk factors associated with drug allergy with a standard questionnaire to be answered by the participants.

**Methods:** In this study, we prepared and administered a questionnaire to inquire about drug allergy, recurrence of allergy, clinical findings, treatment for allergy, and accompanying comorbidities in outpatients admitted to the internal medicine clinic.

**Results:** A total of 261 (138 men and 123 women) participants were included in this study. The prevalence of drug allergy was 36.8% in the study. It was observed that the most common cause of drug allergy was antibiotics (22.7%), acetylsalicylic acid (antipyretic drugs) (14.4%), and gastric protectors (10.3%). Among the allergic symptoms, urticaria (24.7%) stands first, angioedema (23.7%) second, and hematological problems third (15.5%). The fourth and the fifth are eye findings (13.4%) and skin findings (12.4%), respectively. The history of asthma and drug allergy in first-degree relatives was significantly higher in the group with drug allergy ( $p < 0.001$ ). Male gender, latex allergy, asthma, atopic dermatitis, allergic rhinitis, chronic sinusitis, diabetes, and recurrent urinary tract infection were risk factors associated with drug allergy.

**Discussion and Conclusion:** In this study, the prevalence of drug allergy was found to be 36.8% in patients who applied to the Internal Medicine Clinic. It has been observed that male gender may be associated with drug allergy along with some chronic diseases.

**Keywords:** Acetylsalicylic acid; Antibiotics; Drug allergies; Hypersensitivity reactions

**A**dverse drug reactions are a serious public health problem that affects a physician's prescriptions and practice. Unintended and harmful effects that occur in

normal doses used in humans are defined as drug allergies by the World Health Organization.<sup>[1]</sup> They are examined in two main groups: Type A and Type B reactions.

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Type A reactions are dose-dependent and predictable reactions that can also be seen in normal individuals. Type B reactions, on the other hand, are dose-independent and unpredictable reactions that are seen in susceptible individuals. They are also called drug hypersensitivity reactions.<sup>[2]</sup> Drug hypersensitivity reactions are further divided into two subgroups: allergic and nonallergic.<sup>[3]</sup>

The data on the actual frequency of hypersensitivity reactions with drugs are limited because the diagnosis is often based on patient history and is not supported by diagnostic drug tests, studies are mostly conducted in selected patient groups or specific reaction types, and standard questionnaires or tests are not used in the evaluation.<sup>[4]</sup> There are no clear data on the incidence of drug hypersensitivity reactions in the general population. The frequency of patient-reported drug allergy varies widely in different populations and settings, with rates as high as 39%.<sup>[5]</sup>

The drugs that most commonly cause drug hypersensitivity reactions are beta-lactam antibiotics and nonsteroidal anti-inflammatory drugs, which do not seem to have changed their prevalence over the years.<sup>[6]</sup> Factors causing drug hypersensitivity reactions are drug-related factors (structural characteristics of the drug, route of administration, frequency of administration, and, frequency of consumption), individual-related factors (gender, age, individual drug allergy history, family history, and atopy), and genetic risk factors.<sup>[7]</sup>

The data on hypersensitivity reactions to drugs in the adult population are scarce in Türkiye. This study aimed to determine the prevalence of self-reported drug hypersensitivity reactions and related factors among adults in Türkiye, using questionnaires to be answered by the patients.

## Materials and Methods

This study was planned as a prospective study in the Internal Medicine Clinic. The study was designed in accordance with the Declaration of Helsinki and the Good Clinical Practice Guidelines. The study was approved by the Local Ethics Committee (Date: March 10, 2021; No.: E2. Kurul-E2-21-271).

Volunteers over the age of 18 years who applied to the Internal Medicine Clinic for any reason were included in the study. Those who did not want to participate in the study and did not fill out the questionnaires were excluded from the study. A standard questionnaire consisting of 16 questions about the allergy history, concomitant diseases, family history, and drug history of the patients was administered to all participants included in the study.

## Statistical Analysis

Statistical analysis was conducted using IBM SPSS Statistics Version 26.0 for Windows (IBM Corp., Armonk, NY, USA). Numerical variables were shown as mean±standard deviation (min–max). Categorical variables were expressed as numbers and percentages. Pairwise comparisons of continuous variables were made with Student's t-tests. The Chi-squared test and Fisher's exact test were used to compare categorical variables. Parameters found to be significant at the level of  $p < 0.2$  for drug allergy in the univariate analysis were included in the multivariate stepwise logistic regression analysis to identify independent predictors. In the multivariate analysis, the odds ratio was calculated with 95% confidence intervals for these parameters. The multivariate model's goodness of fit was assessed by performing the Hosmer–Lemeshow test. A value of  $p < 0.05$  (two-sided) was considered statistically significant in all analyses.

## Results

A total of 261 (mean age:  $43.5 \pm 12.6$  years) adults, 123 (47.1%) women and 138 (52.9%) men, participated in our study. The self-reported drug allergy prevalence of the patients who applied to the outpatient clinic was 36.8% (96/261). The clinical and demographic findings of the study population are summarized in Table 1. The median age (46.7 vs 41.6 years;  $p = 0.002$ ) and the median rate of asthma diagnosis (37 vs 14;  $p < 0.001$ ) were higher in the group that defined drug allergy compared with the group that did not. Diabetes (24% vs 9.1%;  $p = 0.001$ ), chronic sinusitis (11.5% vs 3.6%;  $p = 0.014$ ) renal failure (7.3% vs 1.8%;  $p = 0.041$ ), and recurrent urinary tract infections in the drug-allergic group compared with the nonallergic group infection rate (6.3% vs 0.6%;  $p = 0.011$ ) was found to be higher. The rate of drug allergy in first-degree relatives was higher in the drug-allergic group (40.6% vs 17%;  $p < 0.001$ ).

The independent risk factors reported for drug allergies were male gender, asthma, allergic rhinitis, latex allergy, atopic dermatitis, diabetes, chronic sinusitis, and recurrent urinary tract infection (Table 2). The most common allergic symptoms experienced by the patients with drugs were urticaria (24.7%), angioedema (23.7%), hematological problems (15.5%), eye discharge (itch and redness) (13.4%), and other skin findings (12.4%). The most frequently accused drugs were antibiotics (22.7%), aspirin/other pain relievers (antipyretics) (14.4%), and gastric protectors (10.3%) (Table 3). It was determined that the group defining drug allergy most frequently was the 21–30 age group. We found that the most common drug allergy was due to orally taking drugs (64.2%).

**Table 1.** Clinical demographic findings of the study population

Variables	Study population (n=261)		Defining drug allergy (n=96)		No drug allergy (n=165)		p
	n	%	n	%	n	%	
Gender (female)	123	47.1	31	32.3	92	55.8	<0.001
Age (years)	43.5	18–80	46.7	21–80	41.6	18–73	0.002
Level of education							0.109
Illiterate	20	7.6	8	8.3	12	7.3	
Primary education	87	33.3	39	40.6	48	29.1	
High school	100	38.3	37	38.5	63	38.2	
University	47	18	11	11.5	36	21.8	
Concomitant allergic disease							
None	134	51.3	20	20.8	114	69.1	<0.001
Asthma	51	19.5	37	38.5	14	8.5	<0.001
Allergic rhinitis	18	6.9	10	10.4	8	4.8	0.087
Food allergy	13	5	6	6.3	7	4.2	0.472
Chronic urticaria	17	6.5	6	6.3	11	6.7	0.895
Bee allergy	15	5.7	6	6.3	9	5.5	0.790
Latex allergy	11	4.2	8	8.3	3	1.8	0.021
Atopic dermatitis	10	3.8	6	6.3	4	2.4	0.179
Concomitant chronic disease							
None	115	44	16	16.7	99	60.0	<0.001
Hypertension	23	8.8	6	6.3	17	10.3	0.265
Diabetes	38	14.6	23	24.0	15	9.1	0.001
Heart disease	15	5.7	7	7.3	8	4.8	0.413
Goiter	18	6.9	8	8.3	10	6.1	0.485
Migraine	22	8.4	5	5.2	17	10.3	0.153
Chronic sinusitis	17	6.5	11	11.5	6	3.6	0.014
Renal failure	10	3.8	7	7.3	3	1.8	0.041
Liver failure	8	3	6	6.3	2	1.2	0.054
Recurrent urinary tract infection	7	2.7	6	6.3	1	0.6	0.011
Cystic fibrosis	7	2.7	5	5.2	2	1.2	0.104
Presence of drug allergy in first-degree relatives	67	25.7	39	40.6	28	17.0	<0.001

## Discussion

In this study, we aimed to determine the frequency of drug allergy and the risk factors associated with drug allergy in patients who applied to the Internal Medicine Outpatient Clinic in a different area from the allergy clinic. Drug allergy is the abnormal response of the immune system to drugs, together with structural differences. These are called hypersensitivity reactions. It is not possible to predict in advance whether a drug-induced allergy will develop. However, it is useful to be cautious about some allergic bodies and drugs with high drug allergies because these people have a high risk of developing drug allergies.

The prevalence of drug allergy varies widely in population-based studies. Hastanede yapılan çalışmaları inceledik. In a study conducted by Allain et al.<sup>[8]</sup> on 550 patients, the fre-

quency of drug allergy was found to be 5.6%. A study by Bigby et al.<sup>[9]</sup> on 15 438 patients found the frequency of drug allergy to be 2.2%. Classen et al.,<sup>[10]</sup> in their study performed on 36 653 patients, found the frequency of drug allergy to be 1.8%. In a study conducted by Hunziker et al.<sup>[11]</sup> on 48 005 patients, the frequency of drug allergy was found to be 2.7%. We examined prevalence studies in outpatients. In a cross-sectional, observational prospective epidemiological study conducted in Spain in 2005, the rate of drug allergy was found to be 26.6%.<sup>[12]</sup> In a study conducted by England et al.<sup>[13]</sup> in the USA, consultations applying to the allergy immunology clinic between 1987 and 2001 were examined, and the frequency of drug allergy was found to be 36% in this study. In a systematic review and meta-analysis, 53 studies including 126 606 patients were analyzed. In this meta-analysis, the fre-

**Table 2.** Risk factors associated with drug allergy

Risk factor	RR (95% CI)	p
Male	2.389 (1.214–4.700)	0.012
Asthma	11.883 (5.216–27.073)	<0.001
Allergic rhinitis	7.179 (2.333–22.090)	0.001
Latex allergy	15.956 (3.545–71.812)	<0.001
Atopic dermatitis	8.313 (1.913–36.128)	0.005
Diabetes	3.917 (1.614–9.507)	0.003
Chronic sinusitis	4.395 (1.105–17.481)	0.036
Liver failure	7.914 (1.245–50.325)	0.028
Recurrent urinary tract infection	19.436 (1.720–219.631)	0.016

RR: Relative risk; CI: Confidence interval.

quency of medication was found to be 8.3%.<sup>[14]</sup> In different studies, the frequency of drug allergy has been shown to be as high as 39%.<sup>[5]</sup> In our study, the frequency of drug allergy was found to be 36.8% in the survey study conducted on patients who applied to the Internal medicine outpatient clinic.

In our study, the rate of asthma was found to be higher in the group with drug allergy. When we look at the studies, asthma does not directly trigger drug allergy, but it is associated with atopy and allergy, and therefore, the rate of asthma may be found to be high in cases with drug allergy.<sup>[15]</sup> In addition, the rate of diabetes, renal failure, chronic sinusitis, and recurrent urinary tract infections was found to be higher in the group with drug allergy compared with the other group in our study. Concomitant comorbidities may predispose to the development of allergic drug reactions by altering metabolic pathways and triggering changes in immunological responses to drugs. Diabetes is a chronic condition that affects both metabolic pathways and the immune system. Likewise, there may be variability in the immune response in conditions such as renal failure and infective conditions such as chronic sinusitis and urinary tract infection. In our study, the male gender was found to be associated with drug allergy. However, when the studies in the literature were examined, the rate of drug allergy was found to be higher in females compared with males.<sup>[16–19]</sup> The small sample size in our study may have caused this result. Apart from this, atopic dermatitis, latex allergy, and allergic rhinitis were found to be other factors associated with drug allergy in our study. The relationship of these diseases with drug allergy has not been fully revealed. However, as we know, there are two factors associated with drug allergy. The first is drug-related factors and the other is host-related factors. When we look at atopic dermatitis, latex allergy, and allergic rhinitis, which were found to be associated with drug allergy in our study, we

**Table 3.** Clinical findings in patients with drug allergy

Variables	Defining drug allergy (n=96)	
	n	%
Symptoms and signs in patients with drug allergy		
Itchy red bumps	24	24.7
Swelling without itching	23	23.7
Other skin findings	12	12.4
Cough, shortness of breath, wheezing	11	11.3
Throat congestion, difficulty speaking, difficulty swallowing	4	4.1
Sneezing, itchy nose, runny nose, stuffy nose	8	8.2
Eye discharge, itching, redness	13	13.4
Heart palpitation	2	2.1
Stomach pain, nausea, vomiting, diarrhea	4	4.1
Hypotension	5	5.2
Inflamed kidney	3	3.1
Vasculitis	5	5.2
Serum disease	8	8.2
Hematological problems (anemia, leukopenia, thrombocytopenia)	15	15.5
Total number of drug allergies experienced		
1	31	32.6
2–3	49	51.6
More than 4	15	15.8
Reuse of the drug that caused the allergy		
Yes	35	36.8
Presence of similar complaints in the reuse of the drug that caused the allergy		
Yes	2	5.7
Drugs that cause allergic reactions and their frequency		
Antibiotic	22	22.7
NSAID	14	14.4
Muscle relaxants	8	8.2
Flu medicine	7	7.2
Stomach protectors	10	10.3
Radiocontrast agent	2	2.1
LA/GA	4	4.1
Insulin	4	4.1
Vaccines	5	5.2
Unknown	26	26.8
Age at first drug allergy		
0–10 year	10	13.7
11–20 year	15	20.5
21–30 year	24	32.9
31–40 year	14	19.2
41–50 year	7	9.6
51–60 year	3	4.1
>60 year	0	0
Way of taking the drug		
Oral	61	64.2
Intramuscular injection	2	2.1
Intravenous injection	27	28.4
On the skin	1	1.1

NSAID: Non steroidal anti inflammatory drugs; LA/GA: Local anesthetics/General anesthetics.

can say that there is a predisposition to allergy in the host and a weakness in the immune system in all three cases.

In our study, the most common symptoms associated with drug allergy were urticaria, angioedema, hematological problems, eye discharge (itching and redness), and other skin findings. When we look at the studies in the literature, urticaria, angioedema, eye discharge (redness and itching), and skin lesions are at the forefront.<sup>[20–22]</sup>

In our study, it was observed that the most common drugs causing drug allergy were antibiotics, aspirin/other pain relievers, antipyretics, and stomach protectors. In the analysis of spontaneous drug hypersensitivity reactions collected by the Italian Interregional Pharmacovigilance Group in seven regions of Italy, antibiotics were found to be the most common drug causing drug allergy. NSAIDs ranked second.<sup>[23]</sup> Antibiotics, especially beta-lactam antibiotics,<sup>[24]</sup> take the first place in drug allergies.<sup>[25]</sup> NSAIDs are in second place after antibiotics.<sup>[16,17,26,27]</sup> Apart from these, drug allergies due to gastric protectors are not to be underestimated.<sup>[28–30]</sup>

A prospective cross-sectional survey is the possible main limitation of our study. However, another limitation is that it was conducted with a limited number of participants. The fact that our results are similar to the literature data shows that these limitations are minimized.

## Conclusion

In this survey study, we found that the self-reported drug allergy prevalence of the patients who applied to the outpatient clinic was 36.8%, and drug allergies most frequently developed with antibiotics and aspirin/other pain relievers (antipyretics). There is a need for more comprehensive studies on the frequency of drug allergy and related factors in the adult population.

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**Conflict of Interest:** None declared.

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