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Adverse reactions during drug challenges: a single US institution's experience

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ABSTRACT

Background: Drug challenge is a useful tool when diagnostic testing lacks predictive value for a questionable history of drug allergy. Placebo-controlled drug challenge studies demonstrate that a significant number of patients report purely subjective symptoms to placebo.
Objective: To evaluate the safety and rate of adverse effects when performing drug challenges and to identify predictive factors for occurrences of subjective symptoms during drug challenges.
Methods: We performed a 6-year, retrospective medical record review of patients who underwent drug challenges by members of the Allergy and Immunology Division after consultation deemed drug challenges to be appropriate. Statistical analysis was performed to compare the proportion of patients with subjective symptoms based on certain factors, including sex, age, number of listed drug allergies, interval from historical drug reaction to the drug challenge, and types of historical reaction.
Results: A total of 114 patients underwent 123 drug challenges. Only 1 patient was deemed to have a true positive drug challenge result. Twenty patients reported subjective symptoms during graded challenge, all of which were not deemed a positive challenge. There was a significantly higher proportion of patients who reported subjective symptoms in females, those with a higher number of listed drug allergies, and those whose historical reactions were primarily subjective in nature.
Conclusion: Drug challenges are safe procedures in appropriately selected patients. A number of patients report subjective symptoms during drug challenges. Identifying patients at high risk for subjective symptoms may assist in determining whether placebo-controlled drug challenges should be performed.

Introduction

Drug challenge is a useful tool when diagnostic testing lacks predictive value for a questionable history of drug allergy.[1] The most common form of drug challenge is a graded challenge. Graded challenge is used to determine whether a patient will have an adverse reaction to a drug by administering lower than therapeutic doses for a period with observations for reactions. A typical starting dose for a graded challenge is 1/100th or 1/10th of the final dose of the drug. Graded challenge is intended for patients who are unlikely to be allergic to the given drug. The benefit of a drug challenge is that it can eliminate the need for drug desensitization and can shorten the patient's time to receiving the necessary medication and omitting the requirement for repeat desensitization if the drug is required in the future.

Placebo-controlled drug challenge has a role in drug challenges when one suspects a high likelihood of a nocebo effect, which is defined as the occurrence of untoward reactions after the administration of an indifferent substance or placebo. A study of 600 patients in Italy who underwent a masked oral challenge found the overall occurrence of a nocebo effect to be 27%.[2] A later study in Brescia, Italy, reported that the nocebo effect occurred in just 3% of their patients.[3]

Certain drug challenges have been documented to be of low risk, and these challenges include the following: (1) patients with negative penicillin skin test results challenged with a penicillin,[4–6] (2) penicillin allergic patients challenged with a cephalosporin[7] or a carbapenem,[8] and (3) local anesthetic challenges.[9,10] Conversely, patients with aspirin-exacerbated respiratory disease (AERD) who undergo aspirin challenge are known to be of high reaction risk.[11,12] In most other cases, the risk of reaction to drug challenges is not well known.

Because the risk of certain drug challenges had not previously been clearly defined, our primary objective was to evaluate the safety of drug challenges performed at our institution. Furthermore, on the basis of our observations in performing drug challenges, many patients seemed to have purely subjective symptoms not consistent with an allergic reaction. Therefore, our secondary objective was to identify predictive factors for occurrences of subjective symptoms during drug challenges. By doing this, we

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hoped to identify a subset a patients in whom a placebo-controlled drug challenge should be considered.

Methods

Study Design

We performed a 6-year, retrospective medical record review of patients with reported drug allergy who underwent drug challenges by members of the Allergy and Immunology Division after consultation deemed drug challenges to be appropriate. The study was approved by the University of Texas Southwestern Institutional Review Board.

Patient Selection

Patients were identified through 3 different screening methods for the period of January 1, 2006, through January 17, 2012: (1) at outpatient clinics of the University of Texas Southwestern hospital system, patients who were evaluated by allergy and immunology adult faculty were screened by *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) codes pertaining to drug reaction or drug allergy (995.20-995.29); (2) at outpatient clinics at Parkland Memorial Hospital in Dallas, Texas, the allergy pharmacist who prepares all drugs and placebo for drug challenges provided a list of patients who underwent drug challenges; and (3) for hospital inpatients at both University of Texas Southwestern and Parkland Memorial Hospital, allergy and immunology fellow procedural logs were reviewed. Patients identified through these 3 screening methods were then evaluated to assess for documented drug challenges. Patients who underwent at least 1 drug challenge were included in the study if they met 1 of the following criteria: (1) challenge was performed to the causal drug or (2) challenge was performed to a different drug within the same class. Patients had to be at least 14 years of age, and only challenges performed in clinics or hospitals were included. Placebo-controlled drug challenges were included in the study.

Exclusion Criteria

Patients were excluded from the study if the following were performed: (1) drug desensitization protocols as defined by the drug allergy practice parameter[1]; (2) history of severe life-threatening reactions (eg, Stevens-Johnson syndrome, toxic epidermal necrolysis, and drug rash with eosinophilia and systemic symptoms syndrome); (3) penicillin skin test before challenge to a β-lactam drug; (4) local anesthetic challenges; (5) patients with AERD who underwent aspirin or nonsteroidal anti-inflammatory drug (NSAID) challenge or desensitization; and (6) patients who were challenged with an unrelated drug (eg, patient with a cephalosporin allergy challenged to a sulfonamide). Skin tests performed with other drugs (a nonpenicillin drug) were included in the study because the utility of skin tests to other drugs has not been validated and has poorly defined specificity and sensitivity.

Drug Challenge Protocols

The protocol for drug challenge was determined based on the decision of the individual faculty members. Types of challenges included placebo-controlled, full dose, and graded challenges. Patients who had convincing histories of anaphylaxis were never challenged to the causative drug. Some patients with convincing histories of anaphylaxis were challenged to drugs within the same class but are structurally different (eg, a different NSAID).

Defining Challenge Outcomes

Outcomes of drug challenges were divided into 2 categories. A positive drug challenge result was defined by either (1) objective findings consistent with an allergic reaction as defined in the drug allergy practice parameter[1] or (2) subjective symptoms consistent with an allergic drug reaction (eg, diffuse pruritus). A negative challenge result was defined by either (1) no symptoms or signs or (2) subjective symptoms not consistent with a drug allergic reaction (eg, isolated tongue itching or headache). In addition, a negative challenge result included patients who were asymptomatic with the full dose of the drug regardless of what symptoms they experienced at lower doses.

Data Collection

Data that were abstracted included patient's sex, age, number of listed drugs allergies in the patient's medical record, interval from historical drug reaction to the drug challenge, and historical presentation of drug reactions.

Historical presentation of drug reactions was subdivided into 12 categories: (1) urticaria, (2) exanthematous rash, (3) other nonspecific rash, (4) pruritus without rash, (5) throat symptom (eg, throat swelling), (6) other angioedema (defined as non–throat-related angioedema), (7) lower respiratory tract symptom, (8) cardiovascular symptom, (9) gastrointestinal symptom, (10) multiorgan system, (11) other, and (12) unknown. Multiorgan system is defined as at least 2 organ systems that are typically involved in allergic reaction (eg, cutaneous and gastrointestinal). In addition, for purpose of statistical analysis, historical presentation of drug reactions was also subdivided into primarily *subjective* and *objective*. *Objective* was defined as reported reactions that are normally visible and include at least 1 of the following: (1) any rash, (2) other angioedema (eg, lip swelling), and/or (3) gastrointestinal symptoms that include vomiting or diarrhea. *Subjective* was defined as reported reactions that are not visible and include any or several of the following: (1) pruritus without rash, (2) throat symptoms, (3) lower respiratory tract symptom (eg, dyspnea), (4) cardiovascular symptom (eg, lightheadedness), and/or (5) gastrointestinal symptoms that consist of abdominal pain or nausea without vomiting or diarrhea. Multiorgan system symptoms were defined as *objective* if they included any 1 symptom that fulfills the criteria (eg, urticaria and shortness of breath). An example of a multiorgan system symptom classified as *subjective* is throat tightness and pruritus without rash. Historical reactions that were unknown were not classified in either the *subjective* or *objective* category.

Occurrence of Subjective Symptoms During Drug Challenges

In certain cases, patients underwent multiple drug challenges. To avoid duplicity of patients in the data analysis, if multiple drug challenges were performed on 1 patient, only the first drug challenge that met both the inclusion and exclusion criteria was included in the analysis. All patients who were deemed to have a negative drug challenge result as defined herein were subdivided into 2 categories: (1) those who experienced subjective symptoms at any step of the drug challenge and (2) those without subjective symptoms. The rate of subjective symptoms for each data variable (eg, sex) was determined by calculating the ratio of positive subjective symptoms to the total number of challenges.

Statistical Analysis

Statistical analysis was performed with SPSS statistical software for Windows, version 17.0. Descriptive findings are presented with medians and proportions. All tests of statistical significance comparing the proportion of patients with subjective symptoms based on demographic and drug reaction characteristics (sex, age group, number of listed drug allergies, interval from historical drug reaction to the drug challenge, and historical reaction) were performed with χ^2 exact tests. $P < .05$ was defined as statistically

significant. The number of listed drug allergies was categorized for statistical testing as 1 to 2 allergies, 3 to 5 allergies, 6 to 10 allergies, and greater than 10 allergies. Age was categorized as 14 to 35, 36 to 50, 51 to 65, and older than 65 years. Classification of historical reactions was collapsed to subjective vs objective for statistical testing (Table 2). Interval from historical reaction to drug challenge was categorized for statistical testing as 0 to 1, 2 to 5, 6 to 20, and more than 20 years.

Results

Baseline Characteristics

Of the medical records screened by *ICD-9-CM* codes at outpatient clinics at University of Texas Southwestern, 1099 records were identified, and 86 patients (94 challenges) met the inclusion and exclusion criteria. An additional 28 patients (29 challenges) at outpatient Parkland clinic and inpatient facilities were identified and met the inclusion and exclusion criteria for the study. Thus, a total of 114 patients were identified.

Table 1 lists the patient demographics. A total of 114 patients underwent at least 1 drug challenge. Patients ranged in age from 15 to 85 years (median age, 54.5 years; interquartile range [IQR], 41.5-65.0 years). Most of these patients were female (75%). The number of listed drug allergies in the medical record ranged from 1 to 24 (median, 3; IQR, 2-5.25).

Historical Drug Reaction

The classification of historical reactions is summarized in Table 2. Of all the historical drug reactions, 45 (37%) were reported as cutaneous symptoms, most of which were classified as other nonspecific rash (n = 21). Multiorgan system (n = 26) was the next most commonly reported historical reaction. Only 6 of these reactions were deemed by our allergists to be likely or possible anaphylaxis. Of these, 5 were challenges to a different NSAID (n = 4) or different fluoroquinolone (n = 1). One of them was a "questionable" anaphylaxis to acetaminophen (patient reported nonspecific rash and shortness of breath and was brought to the emergency department but was not admitted), and a drug challenge was performed because acetaminophen allergy is extremely rare. Thirteen reactions (10.6%) were reported as isolated throat symptoms, which included throat tightness, closure, or swelling. Twelve reactions (9.8%) were reported as patients not being able to recall their reaction. Only a few of the reactions were reported as isolated cardiovascular or lower respiratory tract symptom. None reported isolated gastrointestinal symptoms.

Characteristics of Challenges

Table 3 lists the characteristics of the drug challenges. A total of 124 challenges were performed. A total of 102 challenges (82.9%) were open challenges, and 21 (17.1%) were single-blind, placebo-controlled challenges. Only 5 challenges (4.1%) involved antecedent skin testing to the drug, none of which were penicillin skin testing. Ninety-eight challenges (79.7%) were to the same drug to which the patient had a previous reaction. The remaining 25 challenges (20.3%) were to a different drug within the same class. Of these, 13 (10.6%) were to a different fluoroquinolone, 7 (5.7%) to a different NSAID, 4 (3.3%) to a different cephalosporin, and 1 (0.8%) to a different insulin. Eighty-three challenges (67.5%) were to antibiotics, most of which were to penicillin (35%). Most challenges to penicillin were performed during the period that the penicillin major determinant was not commercially available (2006-2010).

Table 1
Patient characteristics

Characteristic	No. (%) of patients (N = 114)
Sex	
Female	85 (74.6)
Male	29 (25.4)
Age range, y	
14-35	25 (21.9)
36-50	23 (20.2)
51-65	38 (33.3)
>65	28 (24.6)
No. of listed drug allergies	
1-2	47 (41.2)
3-5	39 (34.2)
6-10	14 (12.3)
>10	14 (12.3)

Table 2
Classification of historical reactions and frequency of subjective symptoms with drug challenge

Historical drug reaction	No. of historical reactions challenged	No. (%) with subjective symptoms
Total	123	20
Subjective	29	10[a] (34)
Pruritus without rash	5	1
Throat symptom	13	4
Lower respiratory symptom	4	2
Cardiovascular symptom	2	1
Multiorgan system	4	2
Other	1	0
Objective	82	10[a] (12)
Urticaria	16	0
Exanthematous rash	8	1
Other nonspecific rash	21	4
Other angioedema	13	0
Multiorgan system	22	5
Other	2	0
Unknown	12	0

[a] $P = .01$.

Table 3
Drug challenge characteristics

Characteristic	No. (%) of patients
Total No. of challenges	123
Types of challenges	
Open	102 (82.9)
Single-blinded, placebo-controlled	21 (17.1)
Skin testing performed before challenge	5 (4.1)
Challenges to	
Same drug to which the patient had a historical reaction	99 (80.5)
Different fluoroquinolone	11 (8.9)
Different NSAID	7 (5.7)
Different cephalosporin	5 (4.1)
Different insulin	1 (0.8)
Challenges performed to	
All antibiotics	83 (67.5)
Penicillin	43 (35.0)
Cephalosporin	9 (7.3)
Fluoroquinolone	15 (12.2)
Sulfonamide	8 (6.5)
Other antibiotic	8 (6.5)
NSAID	17 (13.8)
Other analgesic	5 (4.1)
Corticosteroid	2 (1.6)
Insulin	4 (3.3)
Other	12 (9.8)
Interval from historical drug reaction to drug challenge, y	
0-1	27 (22.0)
2-5	21 (17.1)
6-20	26 (21.1)
>20	40 (32.5)
Unknown	9 (7.3)

Abbreviation: NSAID, nonsteroidal anti-inflammatory drug.

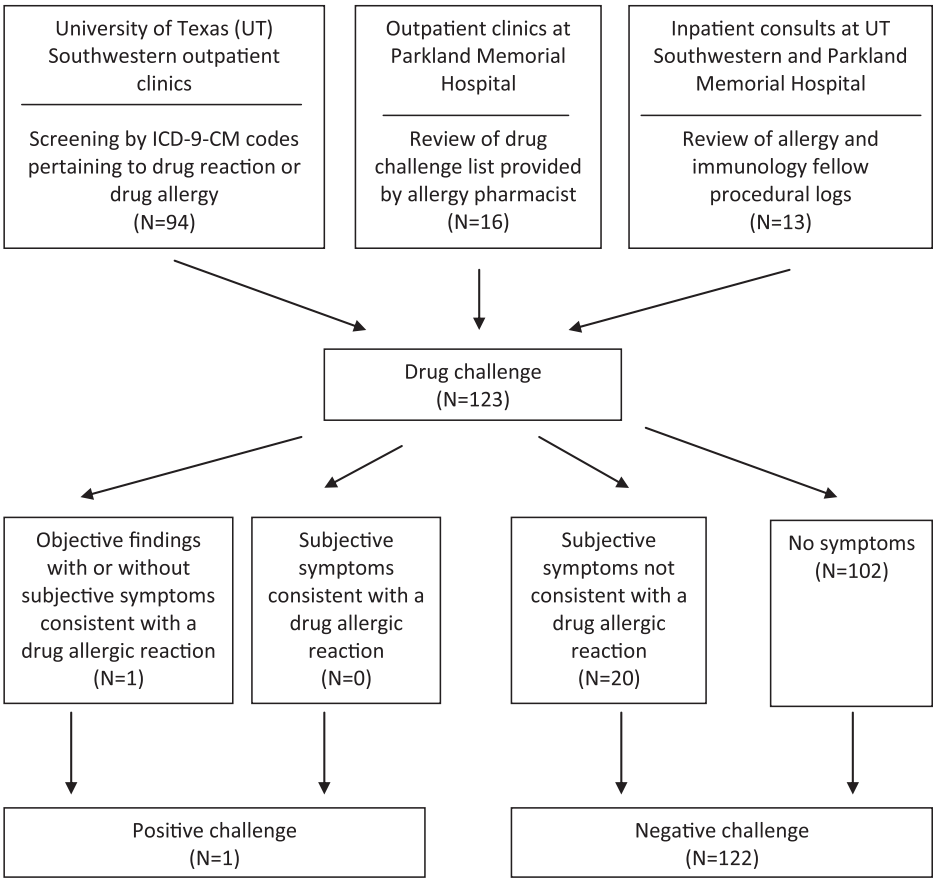

Figure 1. The 3 screening methods to ultimately accrue a list of drug challenges that fulfills the inclusion and exclusion criteria for the study. The bottom half of the flow diagram illustrates the 4 general outcomes of drug challenges, which are then ultimately categorized into positive and negative challenge results.

Challenge Outcomes

Figure 1 outlines the challenge outcomes. A total of 102 (82.9%) of the challenges were completed without any symptoms.

Only 1 patient was believed to have had a positive drug challenge result. This patient's historical reaction was a pruritic "measles-like" rash to cephalexin. She was challenged to cefuroxime without immediate symptoms. However, 18 hours later, she reported a pruritic rash that was similar to the reaction to cephalexin. She did not return to the clinic for confirmation of the rash.

In the remaining 20 challenges (16.3%), subjective symptoms were reported at some point during the graded challenge, all of which were deemed not to have been allergic reactions. Of these, 14 subjective symptoms were reported only during the early steps of the graded challenge or to placebo without symptoms to the full dose of the drug. In 6 challenges, subjective symptoms were reported at the final dose; none of these patients were deemed to have symptoms consistent with a true allergic reaction. Five of these 6 patients reported symptoms at earlier doses. Reported symptoms at the full dose of the drug included localized itching (eg, itchy ears), face swelling without signs of swelling, and nonspecific dizziness with normal blood pressure. One patient in particular reported sensation of throat tightness with a full dose of acetaminophen; on examination, her lungs were clear to auscultation, and laryngoscopy did not show evidence of laryngeal edema.

Challenge Outcomes to a Different Drug Within the Same Class

All 11 challenges performed to a different fluoroquinolone did not result in any reaction or subjective symptoms. All 7 challenges performed to a different NSAID did not result in any reaction or subjective symptoms. Only 1 of 5 patients who were challenged to a different cephalosporin had a reaction consistent with a possible delayed reaction, as previously mentioned. One challenge performed to a different insulin did not result in any reaction or subjective symptoms.

Predictive Factors for Subjective Symptoms

A larger proportion of female patients experienced subjective symptoms during drug challenges than males (21% vs 3%, $P = .040$).

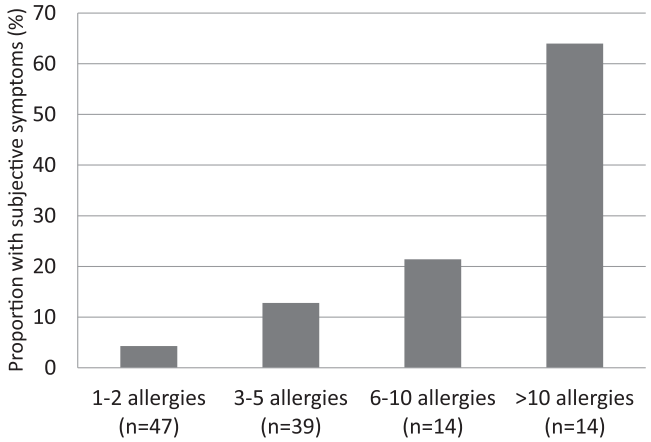

Figure 2. Proportion of patients with subjective symptoms by number of listed drug allergies ($P < .001$).

In a stepwise fashion, there was a systematically larger proportion of patients who experienced subjective symptoms as the number of listed drug allergies increased ($P < .001$) (Fig 2). Patients with greater than 10 listed drug allergies had a 3-fold greater proportion of subjective symptoms than in the next highest group (6-10 listed drug allergies). The proportion of patients with subjective symptoms did not differ based on age group ($P = .57$) and interval from historical drug reaction to the drug challenge ($P = .54$).

Table 2 outlines subjective symptoms subdivided by classification of historical reactions. Subjective symptoms during drug challenges occurred more frequently in patients with historical reactions classified as *subjective* compared with those with reactions classified as *objective* (Table 2: 34.4% vs 12.2%, P=.01). In particular, subjective symptoms appeared to be more frequent in patients whose historical reactions were classified as throat symptom, multiorgan system, lower respiratory tract symptom, and cardiovascular symptom. No subjective symptoms were reported in patients whose historical reactions were classified as urticaria, other angioedema, other, or unknown.

Placebo-Controlled Challenges

Nineteen patients underwent 21 single-blind, placebo-controlled drug challenge. The median number of placebo steps (steps at which only placebo was given) performed per challenge was 3 (IQR, 2-4) and ranged from 1 to 6 steps. Twelve of the 21 challenges (57%) resulted in subjective symptoms to the placebo drug. Most experienced subjective symptoms within the first 2 steps of the challenge (8 with the first step and 3 with the second step), and 1 patient experienced symptoms at the fourth step. The patients chosen to undergo these challenges were all female. Most patients (53%) had at least 6 listed drug allergies. In contrast, only 12% of all patients in this study had at least 6 listed drug allergies. A relatively high proportion of these challenges were performed on patients whose historical reactions were throat symptoms (n = 6) or multiorgan system (n = 7) and patients who reported isolated lower respiratory tract symptoms or isolated cardiovascular symptoms.

Discussion

The goal of our study was to evaluate the safety of drug challenges in cases where the risk of reaction was not previously clearly defined. For that reason, we excluded from our study drug challenges that have already been documented to be of low risk (eg, patients with negative penicillin skin test results challenged with a penicillin) and high risk (eg, AERD patients challenged with an NSAID).

Our results demonstrate that drug challenges in appropriately selected patients are safe. Of a total of 114 patients and 124 challenges, only 1 challenge was deemed to have resulted in a likely positive reaction, which was mild and untreated. The frequency of positive drug challenge reactions in our study is comparable to the results in the study by Ramam et al[13] but is much lower than most other reported drug challenge studies.[14–16] The reason for the difference is that several institutions performed drug challenges to causal drugs in which drug hypersensitivity was suspected.[15,16] In addition, the other common theme in other drug challenge studies is the high prevalence of positive reactions to NSAIDs.[15] In our study, we carefully performed NSAID challenges with the causal drug only in cases in which the history is not consistent with a high likelihood of immediate hypersensitivity reaction (eg, anaphylaxis). Otherwise, in cases of suspected immediate hypersensitivity to a particular NSAID, we performed drug challenges with a different NSAID (eFig 1).

Another reason for our low challenge reaction rate was our stringent criteria for defining a positive challenge result. In a situation when a drug challenge resulted in only subjective symptoms, we carefully evaluated the patient and classified each reaction as a positive or negative challenge result, depending on whether symptoms were (1) consistent with an allergic reaction, (2) reported with placebo, or (3) to the lower dose and not to the full dose of the drug. In patients who report isolated throat symptoms during drug challenge, especially to the full dose of the drug and in the absence of stridor or wheezing on examination, we advocate rhinolaryngoscopy to confirm or rule out laryngeal edema.

Data on cross-reactivity among fluoroquinolones are limited. Dávila et al[17] concluded that cross-reactivity among fluoroquinolones is high, with all 3 patients in their study reacting to a different fluoroquinolone. González et al[18] concluded that there was high degree of cross-reactivity among fluoroquinolones, but the conclusion was based on skin test results rather than drug challenge results. A more recent study found a lower rate of cross-reactivity of fluoroquinolones in patients who experienced immediate-type reaction with the use of oral drug challenges.[19] In our study, most of our patients who reported reactions to fluoroquinolones had either unknown symptoms (n = 2) or cutaneous symptoms not consistent with urticaria (n = 6). Three patients reported symptoms consistent with immediate hypersensitivity, with 1 symptom deemed to be likely anaphylaxis. All 11 challenges to a different fluoroquinolone resulted in a negative reaction, thus providing further evidence that cross-reactivity among fluoroquinolones may not be as high as previously reported.

In our study, 7 drug challenges were performed with a different NSAID from the causal drug. None of the challenges were performed in patients who were suspected to have AERD. Five were performed on patients with a historical reaction consistent with probable or possible anaphylaxis, and the other 2 historical reactions were angioedema. All 7 of these challenges did not result in any reaction or subjective symptoms. Our findings are consistent with prior studies demonstrating that patients with anaphylactic reactions to an NSAID generally tolerate other NSAIDs, suggesting a drug-specific IgE-mediated response.[20,21]

Although only 1 of 124 total drug challenges resulted in a positive challenge result, a fairly substantial proportion of our patients (16.3%) reported subjective symptoms not consistent with an allergic reaction. This finding was similar to a study from India in which 13.4% of drug challenges resulted in subjective symptoms.[13] We investigated further to determine predictive factors for subjective symptoms. On the basis of the results of our study, we found that one of the predictive factors for subjective symptoms was female sex. Prior studies evaluating nocebo effect during oral challenge have also found similar findings in that females more often than males reacted to placebo.[2,3] Another predictive factor is having a large number of listed drug allergies in the medical records, particularly with numbers greater than 10. More than 60% of patients with more than 10 drug allergies reported symptoms during drug challenges. Because of this, we strongly recommend incorporating placebo in this patient population. In contrast, placebo may not be required in patients with a small number (ie, 1 or 2) of listed drug allergies given the very low occurrence (4.3%) of subjective symptoms in this subgroup. In addition, we observed that subjective symptoms were more frequent in patients with historical reactions that were primarily subjective in nature and in particular in those whose historical reactions were throat symptoms, lower respiratory tract symptoms, cardiovascular symptoms, and symptoms that involve the multiorgan system not consistent with anaphylaxis. Age and remoteness of drug reaction do not appear to be predictive factors for subjective symptoms.

This study has several limitations. First, we may not have captured all patients who underwent challenges at our institution, especially in the case of inpatient consultations due to reliance on

allergy fellows' procedural logs. Second, with our method of collecting data, we do not have data on the number of patients who were evaluated but did not undergo challenges. We would estimate that at least 75% of patients we evaluate for drug allergy undergo drug challenges. Third, given the retrospective nature of this study, we may not have accurately classified all historical reactions and often used our best guess based on the documented records. For example, if the rash was not clearly defined based on patient report and/or documentation, we classified the rash as *nonspecific rash*. In addition, remoteness of historical reaction was not captured in all patients because of lack of documentation or poor patient recall. Finally, drug challenges, although generally considered the gold standard in the diagnosis of drug allergy, have limitations, especially with nonimmediate, or delayed, hypersensitivity. In some cases, non-immediate reactions occur only after treatment of several days of the drug at a therapeutic dose.[22] Thus, only a positive challenge result is conclusive, but a negative challenge result is not definitive, especially in nonimmediate drug hypersensitivity.[23]

In conclusion, we found that drug challenges are safe procedures in appropriately selected patients. In addition, the occurrence of subjective symptoms during drug challenges not deemed to be true allergic reactions is not insignificant and, in certain cases (eg, female sex, larger number of listed drug allergies, and historical reactions that are purely subjective in nature), may warrant placebo-controlled challenges.

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Supplementary Data

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.anai.2012.11.007.

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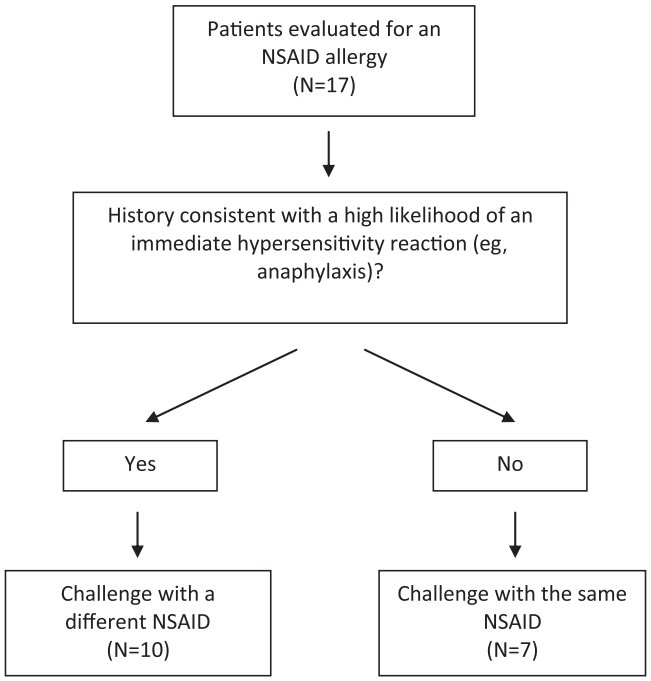

eFigure 1. Approach to patients evaluated with a nonsteroidal anti-inflammatory drug (NSAID) allergy. In cases of suspected immediate hypersensitivity reaction (eg, anaphylaxis) to a particular NSAID, we performed drug challenges with a different NSAID. If the history is not consistent with a hypersensitivity reaction, the patient was challenged with the same NSAID.