

Original Article

Safety, Outcomes, and Recommendations for Two-Step Outpatient Nonsteroidal Anti-Inflammatory Drug Challenges

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What is already known about this topic? Drug challenge protocols to evaluate non-aspirin-exacerbated respiratory disease-related nonsteroidal anti-inflammatory drug (NSAID) hypersensitivity vary widely by provider and institution, and can be prohibitively time- and resource-intensive.

What does this article add to our knowledge? Two-step NSAID drug challenges are safe to perform in the outpatient setting after allergist evaluation. Most patients are then cleared for the use of at least one NSAID.

How does this study impact current management guidelines? Nonsteroidal anti-inflammatory drugs are indicated for many common medical conditions, but therapeutic use can be limited by reported allergy. A simple two-step NSAID challenge protocol may be used in the outpatient setting to de-label appropriate candidates.

BACKGROUND: Nonsteroidal anti-inflammatory drug (NSAID) outpatient challenge protocols are not standardized. They vary in clinical practice and can be time- and resource-intensive to perform.

OBJECTIVE: To investigate the safety and outcomes of two-step outpatient NSAID challenges to evaluate patients with non-aspirin-exacerbated respiratory disease (AERD)-related NSAID hypersensitivity.

METHODS: We conducted a retrospective study of patients with a history of NSAID allergy who underwent outpatient NSAID challenges under allergist supervision. Individuals with AERD were excluded. Patient demographics, NSAID reaction history, and drug challenge details and outcomes were collected. **RESULTS:** A total of 249 patients (mean age, 51.6 years; 63.5% female) underwent 262 NSAID challenges. Of these, 224 challenges were negative (85.5%). Thirty challenges resulted in

an immediate reaction during the challenge procedure (11.5%) and eight resulted in delayed reactions (3.1%). Three individuals with immediate reactions required treatment with intramuscular epinephrine. Factors associated with a positive NSAID challenge included a prior reaction occurring within 5 years of drug challenge (odds ratio [OR] = 3.66; 95% confidence interval [CI], 1.67-8.44), a prior immediate reaction within 3 hours of NSAID ingestion (OR = 2.45; 95% CI, 1.12-5.57), a history of cross-reactive NSAID hypersensitivity to multiple NSAIDs (OR = 2.97; 95% CI, 1.23-6.91), and the presence of comorbid chronic spontaneous urticaria (OR = 2.95; 95% CI, 1.35-6.41). **CONCLUSIONS:** More than 85% of two-step non-AERD NSAID drug challenges were negative for an immediate or delayed reaction, which allowed patients to use at least one clinically indicated NSAID. Challenge reactions were generally mild. Two-step NSAID challenge protocols can be safely performed in the outpatient setting. © 2021 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2021;■:■-■)

Key words: Nonsteroidal anti-inflammatory drug; NSAID; Aspirin; Drug allergy; Adverse drug reaction; Hypersensitivity; Drug challenge; De-labeling

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INTRODUCTION

Adverse reactions to nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly reported in the general population, with a prevalence of 1.5% to 3.5%.^{1,2} However, it is estimated that fewer than 20% of self-reported NSAID adverse reactions are actually consistent with true hypersensitivity³ caused by either immunologic mechanisms or pharmacologic inhibition of cyclooxygenase-1.⁴ Unverified drug allergy labels often persist in the medical record without further investigation or confirmatory

Abbreviations used

AERD- Aspirin-exacerbated respiratory disease
 BWH- Brigham and Women's Hospital
 MGH- Massachusetts General Hospital
 NSAID- Nonsteroidal anti-inflammatory drug

testing,⁵ and allergy labeling has important consequences for prescriber behavior and medication choice.

Nonsteroidal anti-inflammatory drugs are among the most commonly used medications worldwide and are recommended as first-line therapy to manage various conditions including treatment of non-cancer pain^{6,7} and aspirin for acute coronary syndromes.^{8,9} However, allergy overreporting and lack of further investigation may result in unnecessary avoidance of NSAIDs and increased the use of second-line medications. In fact, reported NSAID allergy was recently found to be a risk factor for increased receipt of opioid prescriptions and the development of opioid use disorder in patients with chronic back pain.¹⁰ Careful clarification of NSAID hypersensitivity is therefore critical for patient safety and the initiation of appropriate disease-specific management and treatment.

Diagnosis of NSAID-induced hypersensitivity is based on clinical history in combination with graded drug challenge testing, but can be difficult due to existence of multiple clinical hypersensitivity phenotypes and lack of standardized NSAID drug challenge protocols.¹¹ Specific strategies for aspirin challenge/desensitization for aspirin-exacerbated respiratory-disease (AERD) have been previously reported and these multi-step procedures are typically performed at specialized centers given the high-risk for development of systemic symptoms.¹² For the evaluation of non-AERD NSAID hypersensitivity, however, NSAID challenge protocols vary widely from one to six or more steps with variable dosing intervals, chosen at an individual allergist's discretion based on the patient's clinical history, physician preference, and institutional practices.¹³⁻¹⁵

The goals of this study were to describe the safety and outcomes of a two-step NSAID challenge protocol and to provide recommendations for evaluating non-AERD NSAID allergy in a monitored outpatient setting.

METHODS

Study cohort

Individuals who underwent a two-step outpatient NSAID challenge for any indication excluding AERD evaluation at Massachusetts General Hospital (MGH) or Brigham and Women's Hospital (BWH) between January 1, 2010 and May 31, 2021 were eligible for inclusion in this retrospective cohort study. Patients with a known history of nasal polyps and asthma were specifically excluded, to select only for patients with suspected non-AERD NSAID hypersensitivity.

Patient demographic information and clinical characteristics, including medical and allergic comorbidities, details regarding the initial NSAID-induced reaction, and any allergist-supervised drug challenge procedures were collected from the electronic medical record. The participant self-categorized Race was categorized as Asian, Black, other (specific race not specified, Guatemalan, Italian, Puerto Rican, Middle-Eastern, Salvadoran, Honduran, Brazilian, Columbian, Puerto Rican), White, or not specified, and ethnicity was categorized as Hispanic or Latino, non-Hispanic or Latino, or not

specified by the study investigators. Respiratory symptoms included shortness of breath, chest tightness, and wheeze.

Nonsteroidal anti-inflammatory drug challenges

All drug challenges were performed in an unblinded manner consistent with standard of care at our institutions. Specific challenge doses and observation intervals used for two-step NSAID challenges were based on the formulations and doses of each individual NSAID available through institutional pharmacies and at the primary allergist's discretion, although most protocols employed a strategy using a starting dose of 1:10 to 1:4 of the target dose, as is typical for graded challenges to other medications.¹⁶ For aspirin challenge, a target dose of 325 mg instead of 81 mg was commonly chosen (greater than 80% of challenges described in this study) owing to the possible future need for a higher aspirin dose, such as in the context of early management of acute coronary syndromes.¹⁷

The primary outcome was a failed drug challenge, defined as either an immediate reaction (within 3 hours) or a delayed reaction elicited by the NSAID drug challenge. Patients were not taking antihistamines at the time of challenge.

Statistical analyses

All statistical analyses were performed using RStudio Server Pro (version 1.2.5033-1) (RStudio, PBC, Boston, Mass). Continuous variables are expressed as means with SD, and categorical variables as counts with percentages. Comparisons between groups were performed using Student *t* test or Mann-Whitney *U* test, as appropriate for continuous variables, or Fisher exact or χ^2 test for categorical variables. *P* less than .05 was considered statistically significant. This study was approved by the Mass General Brigham Institutional Review Board.

Role of the funding source

The National Institutes of Health had no role in the design, conduct, or analysis of the data or in the decision to submit the manuscript for publication.

RESULTS

Cohort clinical characteristics

We identified a cohort of 249 patients with reported NSAID hypersensitivity who underwent a total of 262 two-step NSAID drug challenges for non-AERD indications during the study period. Most patients were female (*n* = 158; 63.5%) and White (207; 83.1%), mean age 51.6 years (SD, 17.1 years; range, 5-87 years) (Table I). Allergic and medical comorbidities were common and similar between males and females, with the exception of anxiety (21.5% of females vs 9.9% of males; *P* = .02). A history of chronic spontaneous urticaria was reported by 24.5% of the cohort. Primary reasons for NSAID allergy evaluation included analgesic (*n* = 85; 34.1%) and cardiovascular (*n* = 85; 34.1%) indications. Four individuals were evaluated for consideration of aspirin use in high-risk pregnancy. The remainder were referred by a physician or were self-referred in the setting of another indication for aspirin (eg, stroke prevention, anticoagulation), or simply for NSAID allergy de-labeling without a current specific need.

Historical NSAID reaction characteristics

Most patients reported a prior reaction to aspirin (*n* = 122; 49.0%), followed by ibuprofen (*n* = 114; 45.8%) and naproxen (*n* = 37; 14.9%) (Table I). Whereas most patients (*n* = 161; 64.7%) reported only one lifetime reaction to NSAIDs, 42

TABLE I. Cohort characteristics

Characteristic	Entire cohort [‡] (n = 249)	Female (n = 158)	Male (n = 91)
Mean age, y (n [SD])	51.6 (17.1)	51.9 (16.5)	51.1 (18.3)
Ethnicity, n (%)			
Hispanic or Latino	20 (8.0)	12 (7.6)	8 (8.8)
Not Hispanic or Latino	198 (79.5)	126 (79.7)	71 (79.1)
Not specified	31 (12.4)	20 (12.7)	11 (12.1)
Race, n (%)			
Asian	14 (5.6)	9 (5.7)	5 (5.5)
Black	7 (2.8)	4 (2.5)	3 (3.3)
Other (specific race not specified, Guatemalan, Italian, Puerto Rican, Middle-Eastern, Salvadoran, Honduran, Brazilian, Columbian, Puerto Rican)	11 (4.4)	7 (4.4)	4 (4.4)
White	207 (83.1)	131 (82.9)	76 (83.5)
Not specified	10 (4.0)	7 (4.4)	3 (3.3)
Allergic comorbidities, n (%)			
Asthma	78 (31.3)	55 (34.8)	23 (25.3)
Chronic spontaneous urticaria	61 (24.5)	39 (24.7)	22 (24.2)
Non-NSAID drug allergy	146 (58.6)	99 (62.7)	47 (51.6)
Allergic rhinitis	167 (67.1)	106 (67.1)	61 (67.0)
Atopic dermatitis	33 (13.3)	22 (13.9)	11 (12.1)
Medical comorbidities, n (%)			
Cardiovascular disease	45 (18.1)	23 (14.6)	22 (24.2)
Hypertension	99 (39.8)	56 (35.4)	43 (47.3)
Depression	42 (16.9)	30 (19.0)	12 (13.2)
Gastroesophageal reflux disease	63 (25.3)	42 (26.6)	21 (23.1)
Chronic kidney disease	8 (3.2)	3 (1.9)	5 (5.5)
Anxiety [†]	43 (17.3)	34 (21.5)	9 (9.9)
Thyroid disease	28 (11.2)	22 (13.9)	6 (6.6)
Hyperlipidemia	92 (36.9)	52 (32.9)	40 (44.0)
Diabetes	24 (9.6)	14 (8.9)	10 (11.0)
Malignancy	30 (12.0)	18 (11.4)	12 (13.2)
Chronic pain	78 (31.3)	50 (31.6)	28 (30.8)
Reported culprit NSAID, n (%)			
Aspirin	122 (49.0)	71 (44.9)	51 (56.0)
Ibuprofen	114 (45.8)	78 (49.4)	36 (39.4)
Naproxen	37 (14.9)	25 (15.8)	12 (13.2)
History of reaction to acetaminophen, n (%)	9 (3.6)	5 (3.2)	4 (4.4)
History of reaction to cyclooxygenase-2 inhibitor, n (%)	4 (1.6)	4 (2.5)	0
History of cross-reactive NSAID hypersensitivity,* n (%)	38 (15.3)	27 (17.1)	11 (12.1)
Prior NSAID-induced reaction characteristics, n (%)			
Cutaneous symptoms	189 (75.9)	119 (75.3)	70 (76.9)
Respiratory symptoms	40 (16.1)	19 (12.0)	21 (23.1)

NSAID, nonsteroidal anti-inflammatory drug.

*History of reactions to two or more nonselective NSAIDs.

[†]P = .02 between males and females.[‡]Student *t* test or Wilcoxon rank sum test was used for continuous variables and Fisher exact or χ^2 test for categorical variables.

individuals (16.9%) had had three or more prior NSAID reactions. In addition, 38 patients in the cohort (15.3%) had a history of cross-reactive reactions elicited by two or more distinct nonselective NSAIDs before allergy evaluation.

Over one-third of individuals reported recent reactions within 5 years of allergy evaluation (n = 96; 38.6%), whereas 55 (22.1%) had remote reactions that occurred more than 30 years earlier. Timing of prior NSAID-induced symptom onset was reported to have occurred within 3 hours of NSAID ingestion in 44.6% of the cohort; 6.8% reported prior delayed reactions that

occurred 24 hours after medication intake. An additional 38.9% of participants did not recall timing details of the original NSAID reaction.

Most patients (n = 189; 75.9%) reported that the prior NSAID-induced reaction caused cutaneous symptoms involving urticaria, angioedema, or both, including 90 individuals with cutaneous symptom onset within 3 hours, 24 between 3 and 24 hours, 14 with delayed symptoms greater than 24 hours and 60 with unknown timing of reaction. A reaction history involving non-urticarial delayed cutaneous symptoms was present in 29

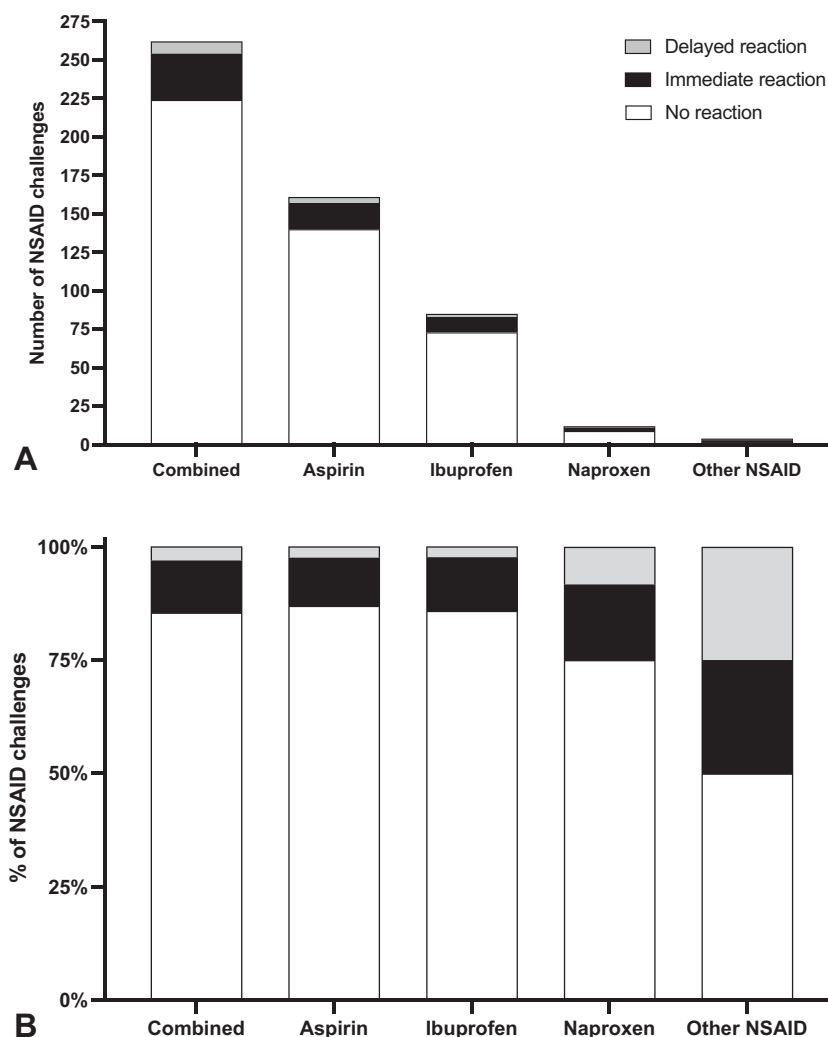


FIGURE 1. Two-step nonsteroidal anti-inflammatory drug (NSAID) challenge outcomes ($n = 262$) by (A) total number of challenges performed and (B) proportion of challenges performed. Overall, 85.5% of challenges were negative with no reaction elicited. Of the 18 of 30 challenges resulting in an immediate reaction after dose 2, most (12 of 18) developed symptoms that began within 60 to 120 minutes of observation. Specific doses were determined by the supervising allergist and according to formulations available from the dispensing pharmacy. Dose ranges for aspirin were 8 to 162 mg for dose 1 and 40.5 to 325 mg for dose 2. Dose ranges for ibuprofen were 4 to 200 mg for dose 1 and 100 to 800 mg for dose 2. Dose ranges for naproxen were 25 to 125 mg for dose 1 and 225 to 500 mg for dose 2. Other NSAIDs included indomethacin (dose 1: 12.5-25 mg; dose 2: 50-75 mg), diclofenac (dose 1: 12.5 mg; dose 2, 37.5 mg), and etodolac (dose 1: 100 mg; dose 2: 100 mg).

individuals (11.6%), with no difference in reporting between sexes.

History of respiratory symptoms elicited by NSAID ingestion was infrequently reported (40 individuals representing 16.1% of the cohort; 23.1% of males vs 12% of females; $P = .03$). Of these 40 individuals, 31 also reported concurrent cutaneous symptoms involving urticaria, angioedema, or both. Only nine individuals experienced isolated respiratory symptoms without cutaneous features during a prior NSAID-induced reaction.

A total of 86 patients (34.5%) reported taking and tolerating at least one other nonselective NSAID since the original NSAID-induced reaction (but not the prior culprit NSAID), before allergy evaluation with drug challenge.

Two-step NSAID challenge outcomes and safety

Among 262 NSAID drug challenges performed in the cohort, most involved administration of aspirin (161), followed by ibuprofen (85), naproxen (12), and other NSAIDs (two indomethacin, one diclofenac, and one etodolac) (Figure 1). Overall, 224 of the NSAID drug challenges were negative (85.5%). Of the remaining challenges, 30 were immediate reactions (11.5%; 17 aspirin, 10 ibuprofen, two naproxen, and one diclofenac) and eight were delayed reactions (3.1%; four aspirin, two ibuprofen, one naproxen, and one indomethacin) elicited after drug challenge.

For the immediate reactions, a minority of reactions (12 of 30) occurred after step 1 (dose 1). Of the reactions elicited after step 2 (dose 2), one-third (six of 18) developed symptoms within the

TABLE II. Factors associated with two-step NSAID challenge-induced reactions

Factor	Negative challenge (n = 224)	Positive challenge* (n = 38)	Odds ratio (95% confidence interval)	P
Age, y (mean [SD])	53.2 (16.7)	47.5 (18.1)		.13
Female, n (%)	144 (64.3%)	23 (60.5%)	1.17 (0.54-2.50)	.72
White race, n (%)	184 (82.1%)	34 (89.5%)	1.84 (0.61-7.56)	.35
Reaction history, n (%)				
Most recent reaction <5 y	80 (35.7%)	25 (65.8%)	3.66 (1.67-8.44)	.0005
Time from ingestion to reaction <3 h	92 (41.1%)	23 (60.5%)	2.45 (1.12-5.57)	.02
Cross-reactive NSAID hypersensitivity†	30 (13.4%)	12 (31.6%)	2.97 (1.23-6.91)	.008
Prior cutaneous symptoms	170 (75.9%)	31 (81.6%)	1.41 (0.56-4.00)	.54
Tolerates ≥1 other NSAIDs	80 (35.7%)	8 (21.1%)	0.48 (0.18-1.14)	.10
Comorbid conditions, n (%)				
Chronic urticaria or angioedema	48 (21.4%)	17 (44.7%)	2.95 (1.35-6.41)	.004
Other (non-NSAID) drug allergy	128 (57.1%)	22 (57.9%)	1.02 (0.48-2.20)	1.0
Asthma	73 (32.6%)	10 (26.3%)	0.74 (0.30-1.67)	.57

NSAID, nonsteroidal anti-inflammatory drug.

Bold value indicates $P < .05$.

*Includes immediate and delayed reactions induced by NSAID challenge.

†History of reactions to two or more nonselective NSAIDs.

first hour after administration of step 2, and 12 of 18 developed symptoms that began 60 to 120 minutes after the administration of step 2 (see [Table E1](#) in this article's Online Repository at www.jaci-inpractice.org).

One-third of the immediate reactions required no treatment. The remaining reactions were managed with antihistamines, leukotriene antagonists, oral corticosteroids, and albuterol, and three patients required clinic-administered intramuscular epinephrine. All three individuals who required epinephrine had a history of chronic spontaneous urticaria and developed symptoms 90 to 110 minutes after the second challenge dose (see [Table E2](#) in this article's Online Repository at www.jaci-inpractice.org). No patients developed hypotension, and all three individuals responded to epinephrine and recovered. Two patients were monitored in the clinic before they were discharged home; one patient was transferred to the emergency room for observation (the reaction occurred in late afternoon near the time when the allergy clinic closed). Two of the three patients had reported an NSAID reaction within 6 months; one had experienced the last reaction 2 years before the drug challenge. Serum tryptase was obtained for two of these individuals treated with epinephrine and was elevated at 15.0 ng/mL (drawn 6 hours after symptom onset; no baseline was available) for one patient, and at 10.3 ng/mL (drawn 2 hours after symptom onset; baseline tryptase of 3.5 ng/mL) for the second patient.

All delayed reactions were managed at home with antihistamines or observation only (see [Table E3](#) in this article's Online Repository at www.jaci-inpractice.org).

Subjective symptoms (eg, nausea, gastrointestinal upset, facial tingling, itching without rash) without evidence of objective findings upon physical examination were reported in 36 challenges. After shared decision making, all patients proceeded to complete the two-step NSAID challenge with no objective signs of a reaction.

Factors associated with positive NSAID challenges

Demographic factors including age, sex, and White race were similar between patients with a negative challenge and those with a positive (immediate or delayed) challenge. History of a reaction

within 5 years of drug challenge (odds ratio [OR] = 3.66; 95% confidence interval [CI], 1.67-8.44), a prior immediate reaction (time from ingestion to symptom onset less than 3 hours) (OR = 2.45; 95% CI, 1.12-5.57), and cross-reactive NSAID hypersensitivity (reactions to two or more nonselective NSAIDs) (OR = 2.97; 95% CI, 1.23-6.91) were all associated with higher risk for a positive drug challenge ([Table II](#)). A history of chronic urticaria and/or angioedema was associated with increased risk for a positive challenge (OR = 2.95; 95% CI, 1.35-6.41); however, other allergic comorbidities such as asthma and the presence of non-NSAID drug allergies were similar between groups.

After the allergy evaluation, 149 individuals in the cohort (59.8%) had the NSAID allergy label completely removed from the medical record. The remaining individuals either were ineligible for de-labeling owing to a failed drug challenge or had a history of multiple NSAIDs to which they reported prior reactions and therefore required additional testing before full NSAID allergy label removal.

DISCUSSION

Overall, we found two-step oral NSAID challenge protocols for evaluation of non-AERD NSAID hypersensitivity to be safe when performed in an outpatient clinical setting with allergist supervision. In the current study population, over 85% of drug challenges were negative with no immediate or delayed reactions elicited. This is comparable to reports of challenge-confirmed NSAID hypersensitivity in the pediatric population.^{15,18}

The timing of reaction has been included in risk stratification algorithms for the evaluation of penicillin allergy.¹⁹⁻²¹ We similarly found the history of a reaction within the preceding 5 years to be associated with increased odds of a positive challenge. Other factors associated with higher risk for a challenge-induced reaction included a prior immediate reaction, cross-reactive NSAID hypersensitivity, and history of chronic spontaneous urticaria. Interestingly, Sanchez et al²² recently reported on a cohort of individuals with well-controlled chronic spontaneous urticaria undergoing NSAID challenges. In that cohort, NSAID

Drug Challenge Protocol		Medication	Potential Challenge Doses*
Step 1	1/10 - 1/4 dose, 60 min observation	Aspirin	40.5mg, 325mg
Step 2	Remainder of dose, 120 min observation	Naproxen	50mg, 500mg
Vitals prior to each step, and after the challenge is complete. Baseline spirometry is recommended for individuals with a history of NSAID-induced respiratory symptoms.		Ibuprofen	60mg, 600mg
Vitals (+/- spirometry) should be repeated at the onset of any symptoms of a reaction.		*Based on standard therapeutic doses and NSAID drug formulations available to the provider	

FIGURE 2. Proposed two-step protocol for outpatient nonsteroidal anti-inflammatory drug (NSAID) drug challenges in patients without aspirin-exacerbated respiratory disease. **(A)** Proposed drug challenge steps and observation periods. **(B)** Suggested challenge doses for common NSAIDs.

challenges conducted while the individuals were not taking antihistamines confirmed NSAID-exacerbated symptoms in 98%. In contrast, 75% of participants were able to tolerate an NSAID challenge while the chronic urticaria was well-controlled on antihistamines, which suggests that the use of antihistamines and clinical control of chronic urticaria symptoms may allow for temporary tolerance of NSAIDs.

For patients with immediate reactions during NSAID challenge, most of those reactions began more than 60 minutes after the administration of dose 2, and the three individuals requiring treatment with intramuscular epinephrine each developed reactions at 90 minutes or more (Table E1). As such, we recommend a simple two-step protocol to evaluate non-AERD NSAID hypersensitivity. Step 1 is one-tenth to one-quarter of the target dose (based on the formulation of the specific NSAID available to the provider) with 60-minute observation, followed by step 2) remainder of the dose with 120-minute observation time. This is the current standard of practice at BWH and MGH for non-AERD NSAID challenges (Figure 2). Multiple factors may influence the specific choice of NSAID used for a drug challenge, including details of the historical NSAID-induced reaction, urgency and current indications for NSAID use, and patient preference or availability if more than one drug challenge is required.

Limitations of the study include the unblinded nature of the drug challenges. However, although the incorporation of placebo into drug challenges has been suggested to reduce false-positive results,²³ this may not be feasible in outpatient practices owing to time and resource constraints. Interestingly, 13.7% of procedures in this study elicited subjective symptoms during the challenge that resolved with observation alone, and all of those individuals proceeded to complete the remainder of the procedure with no additional symptoms. This highlights the importance of distinguishing subjective from objective findings elicited by drug challenge and engaging in shared decision-making with patients to determine benefits versus risks regarding proceeding and completing the drug challenge to definitively rule out hypersensitivity.

The challenges reviewed in this study were performed at two large academic hospitals within a single health care system in the northeastern United States with extensive experience in drug challenges; this experience may not be generalizable to community practice. However, given the familiarity of the MGH and BWH allergist-immunologists, allergy nurses, and ancillary staff

in drug challenge protocols and management of any elicited reactions, we suspect that there is a lower threshold for evaluation with drug challenge (eg, inclusion of more high-risk patients) than in private allergy practice or smaller group practices. This further supports the safety of NSAID allergy evaluation with outpatient drug challenge. There is significant potential benefit related to NSAID allergy de-labeling. We present evidence for the overall low risk for severe reactions induced by NSAID challenge and practical recommendations for a two-step non-AERD NSAID challenge protocol. Altogether, these findings provide guidance and reassurance for the feasibility and safety of two-step NSAID challenges even outside an academic clinical setting.

A simple two-step NSAID drug challenge should be considered for appropriate patients presenting for non-AERD NSAID hypersensitivity evaluation. This can be done safely in the outpatient setting, with a longer observation time after the second challenge dose.

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TABLE E1. Two-step nonsteroidal anti-inflammatory drug challenge characteristics for immediate reactions (n = 30)

Challenge number	Drug	Step 1 dose/step 2 dose (or planned step 2 dose) (mg)	Observation, min			Provocative dose (mg)		Time to reaction after provocative dose, min
			Step 1	Step 2	Provocative step	Step dose	Cumulative dose at time of reaction	
1	Aspirin	40 (325)	120		1	40	40	120
2	Aspirin	40.5 (325)	60		1	40.5	40.5	48
3	Aspirin	40.5 (325)	60		1	40.5	40.5	30
4	Aspirin	81 (325)	60		1	81	81	25
5	Aspirin	81 (325)	90		1	81	81	20
6	Aspirin	162 (325)	60		1	162	162	60
7	Ibuprofen	20 (200)	60		1	20	20	15
8	Ibuprofen	20 (200)	60		1	20	20	43
9	Ibuprofen	60 (600)	60		1	60	60	52
10	Ibuprofen	60 (540)	90		1	60	60	30
11	Ibuprofen	60 (600)	60		1	60	60	37
12	Ibuprofen	100 (300)	60		1	100	100	8
13	Aspirin	40.5/81	60	60	2	81	121.5	60
14	Aspirin	40.5/81	90	90	2	81	121.5	45
15	Aspirin	81/243	60	60	2	243	324	60
16	Aspirin	40.5/325	60	120	2	325	365.5	120
17	Aspirin	40.5/325	60	120	2	325	365.5	42
18	Aspirin	40.5/325	60	120	2	325	365.5	90†
19	Aspirin	81/325	30	60	2	325	406	62
20	Aspirin	81/325	60	60	2	325	406	63
21	Aspirin	81/325	60	60	2	325	406	70
22	Aspirin	81/325	90	90	2	325	406	95†
23	Aspirin*	40.5/325	60	120	2	325	365.5	25
24	Diclofenac	12.5/37.5	30	30	2	37.5	50	41
25	Ibuprofen	20/200	60	60	2	200	220	20
26	Ibuprofen	20/200	90	90	2	200	220	80
27	Ibuprofen	100/300	60	60	2	300	400	65
28	Ibuprofen*	60/600	60	120	2	600	660	10
29	Naproxen	25/225	30	60	2	225	250	45
30	Naproxen	62.5/500	60	120	2	500	562.5	107†

*Same patient.

†Received treatment with intramuscular epinephrine.

TABLE E2. Characteristics of positive challenges (n = 38)

Characteristics	Immediate reaction [‡] (n = 30)	Delayed reaction ^{†,‡} (n = 8)
Signs and symptoms		
Urticaria and/or angioedema	18 (60.0%)	7 (87.5%)
Itching	17 (56.7%)	4 (50.0%)
Flushing	9 (30.0%)	2 (25.0%)
Respiratory symptoms	4 (13.3%)	1 (12.5%)
Felt unwell	4 (13.3%)	0
Nasal congestion, rhinorrhea, itchy nose, or sneezing	4 (13.3%)	0
Dizziness	3 (10.0%)	1 (12.5%)
Headache or facial pain	3 (10.0%)	0
Ocular itching, tearing, or redness	3 (10.0%)	0
Treatment		
Cetirizine	18 (60.0%)	2 (25.0%)
Diphenhydramine	6 (20.0%)	3 (37.5%)
Prednisone	4 (13.3%)	0
Fexofenadine	3 (10.0%)	2 (25.0%)
Epinephrine*	3 (10.0%)	0
Zileuton	2 (6.7%)	0
Montelukast	2 (6.7%)	0
Albuterol	1 (3.3%)	0
No medications or observation only	7 (23.3%)	2 (25.0%)

*In the naproxen challenge (n = 1), symptoms involved progressive urticaria and periorbital angioedema refractory to cetirizine and prednisone. In the aspirin challenge (n = 2), one patient had urticaria, tongue angioedema, and voice changes; the second patient had urticaria, periorbital angioedema, throat tightness, nausea, and mild confusion.

[†]All delayed reactions were managed at home

[‡]Column totals exceed the total number of reactions because patients may have experienced more than one symptom or received more than one treatment medication.

TABLE E3. Two-step nonsteroidal anti-inflammatory drug challenge characteristics for delayed reactions (n = 8)

Challenge number	Drug	Protocol (dose, observation)	Cumulative dose (mg)	Timing*	Reaction symptoms	Treatment [†]
1	Aspirin	40.5 mg, 60 min 325 mg, 120 min	365.5	Same day	Urticaria, flushing, pruritis, chest tightness, tongue itching, and tingling	Cetirizine
2	Aspirin	81 mg, 60 min 325 mg, 60 min	406	Same day	Angioedema (lip)	Cetirizine and fexofenadine
3	Aspirin	81 mg, 60 min 325 mg, 60 min	406	1-3 d	Angioedema (tongue and lips)	Fexofenadine
4	Aspirin	40.5 mg, 90 min 325 mg, 90 min	365.5	>7 d	Angioedema (face), flushing, and pruritis	Observation only
5	Ibuprofen	60 mg, 80 min 600 mg, 110 min	660	3-7 d	Urticaria and pruritis	Diphenhydramine
6	Ibuprofen	200 mg, 30 min 600 mg, 30 min	800	>7 d	Pruritis, nausea/vomiting, and dizziness	Diphenhydramine
7	Naproxen	62.5 mg, 60 min 500 mg, 120 min	562.5	Same day	Urticaria	Diphenhydramine
8	Indomethacin	25 mg, 60 min 75 mg, 60 min	100	1-3 d	Angioedema (right ankle, hand), and joint pain	Observation only

*Same day: 3 to 24 h after completion of drug challenge procedure.

[†]All patients received treatment, including observation only, at home.