

Adverse and Hypersensitivity Reactions to Prescription Nonsteroidal Anti-Inflammatory Agents in a Large Health Care System



Kimberly G. Blumenthal, MD^{a,b,c,d,*}, Kenneth H. Lai, MA^{e,*}, Mingshu Huang, PhD, MA^f, Zachary S. Wallace, MD^{a,c}, Paige G. Wickner, MD, MPH^{c,g}, and Li Zhou, MD, PhD^{c,h,i} Boston, Mass

What is already known about this topic? Nonsteroidal anti-inflammatory drugs (NSAIDs) can cause a variety of adverse drug reactions (ADRs), including side effects as well as allergic or pseudoallergic reactions (hypersensitivity reactions [HSRs]).

What does this article add to our knowledge? A total of 1.7% of patients prescribed diclofenac, indomethacin, nabumetone, or piroxicam have ADRs, of which 18.3% are HSRs. Patients with prior HSRs, female sex, autoimmune diseases, and those prescribed a high NSAID dose have an increased risk of an NSAID HSR.

How does this study impact current management guidelines? Clinician awareness of NSAID hypersensitivity in patients with risk factors can guide patient counseling and safe prescribing practices.

BACKGROUND: Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most frequently used medications in the United States. NSAID use can be limited by adverse drug reactions (ADRs), including hypersensitivity reactions (HSRs). **OBJECTIVE:** We aimed to use electronic health record data to determine the incidence and predictors of HSRs to prescription NSAIDs.

METHODS: We performed a retrospective cohort study of all adult outpatients in a large health care system prescribed diclofenac, indomethacin, nabumetone, or piroxicam between January 1, 2004, and September 30, 2012. The primary outcome was an ADR or HSR attributed to the prescribed NSAID within 1 year of prescription, determined from a longitudinal allergy database. We used natural language processing to classify known ADRs as either HSRs or side effects. Multivariable logistic regression models were used to identify independent risk factors for NSAID HSRs.

RESULTS: Of 62,719 patients prescribed NSAIDs, 1,035 (1.7%) had an ADR, of which 189 (18.3%) were HSRs. Multivariable regression analysis identified that patients with prior drug HSR history (odds ratio [OR] 1.8 [95% CI 1.3, 2.5]), female sex (OR 1.8 [95% CI 1.3, 2.4]), autoimmune disease (OR 1.7 [95% CI 1.1, 2.7]), and those prescribed the maximum standing NSAID dose (OR 1.5 [95% CI 1.1, 2.0]) had increased odds of NSAID HSR. **CONCLUSIONS:** NSAID therapeutic use can be limited by ADRs; about 1 in 5 NSAID ADRs is an HSR. Both patient and drug factors contribute to HSR risk and are important to guide patient counseling. © 2016 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;5:737-43)

Key words: Adverse reaction; Allergy; Drug; Hypersensitivity; Side effect

^aDivision of Rheumatology, Allergy, and Immunology, Department of Medicine, Massachusetts General Hospital, Boston, Mass

^bMedical Practice Evaluation Center, Department of Medicine, Massachusetts General Hospital, Boston, Mass

^cHarvard Medical School, Boston, Mass

^dEdward P. Lawrence Center for Quality and Safety, Massachusetts General Hospital, Boston, Mass

^ePartners HealthCare System, Boston, Mass

^fBiostatistics Center, Massachusetts General Hospital, Boston, Mass

^gDivision of Rheumatology, Allergy, and Immunology, Department of Medicine, Brigham and Women's Hospital, Boston, Mass

^hPartners eCare, Partners HealthCare System, Boston, Mass

ⁱDivision of General Internal Medicine, Department of Medicine, Brigham and Women's Hospital, Boston, Mass

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Corresponding author: Kimberly G. Blumenthal, MD, Division of Rheumatology, Allergy, and Immunology, Medical Practice Evaluation Center, Massachusetts General Hospital, 50 Staniford Street, 9th Floor, Boston, MA 02114. E-mail: kblumenthal1@partners.org.

* These authors contributed equally to this work.

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Abbreviations used

ADR- Adverse drug reaction
 AERD- Aspirin-exacerbated respiratory disease
 COX-2- Cyclooxygenase 2
 EHR- Electronic health record
 HSR- Hypersensitivity reaction
 ICD-9- International Classification of Diseases, ninth edition
 NSAID- Nonsteroidal anti-inflammatory drug
 OR- Odds ratio
 PEAR- Partners Enterprise Allergy Repository
 PHS- Partners HealthCare System
 PO- Oral route

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most widely used medications.¹ NSAIDs can cause a variety of adverse drug reactions (ADRs) that range from minor to severe.²⁻⁴ Reactions to NSAIDs include side effects (eg, gastrointestinal upset, bleeding, nephrotoxicity)^{1,5} as well as allergic or pseudoallergic reactions (ie, hypersensitivity reactions [HSRs]).⁵ Although some side effect reactions do not preclude future use of NSAIDs, HSRs warrant particular caution, as allergic (ie, IgE-mediated) reactions predictably worsen with re-exposure and pseudoallergic reactions often exhibit dose-dependent recurrence.⁶ NSAIDs have been identified as one of the most common causes of drug-induced anaphylactic reactions.^{7,8}

Prior studies suggest a 1.9% to 3.5% prevalence of self-reported allergy to NSAIDs,⁹⁻¹¹ with 2 studies finding self-reported incidence ranging from 0.2% to 6.0%.^{10,12} However, these studies have included all “allergies”—inclusive of both HSRs and side effects—in their frequency estimates. In addition, although electronic health records (EHRs) contain both coded and noncoded (ie, free text) data, prior incidence estimates of NSAID allergy from EHR data used only coded elements, which may have underestimated HSR burden.

Previously reported risk factors for NSAID HSRs include chronic urticaria/angioedema, prior HSRs, aspirin-exacerbated respiratory disease (AERD), and atopy.^{6,13-18} One study using US insurance claims data identified that the NSAID indications of acute pain and inflammatory arthritis increased the risk of NSAID HSRs.¹⁹ In the present study, we applied novel informatics methods using EHR data to estimate the incidence of ADRs and HSRs to prescription NSAIDs, and defined risk factors for developing these HSRs.

METHODS**Study design, population**

We performed a retrospective cohort study using the EHR data available within Partners HealthCare System (PHS), an integrated health care delivery network in the Boston area of the United States. To identify which NSAIDs to use for this study, we first identified the most common NSAIDs in a cross-sectional analysis of the Partners Enterprise Allergy Repository (PEAR), a database of allergy and adverse effect information that contains more than 4 million active allergy records for more than 2 million PHS patients (Table E1, available in this article's Online Repository at www.jaci-inpractice.org).^{11,20} Our analysis focused on NSAIDs that were: (1) prescription-only in the United States, (2) inhibitors of both of the cyclooxygenase 1 and cyclooxygenase 2 (COX-2) enzymes, and (3) used predominantly by the oral route (ie, PO). Diclofenac,

indomethacin, nabumetone, and piroxicam met these criteria and were included in this study.

The study population included all adult outpatients (age ≥ 18 years) prescribed any of the 4 oral NSAIDs from January 1, 2004, through September 30, 2012, and who had at least 1 visit within 1 year at any PHS outpatient clinic after the NSAID prescription.

We subsequently ran a separate analysis of patients prescribed only celecoxib or meloxicam, 2 selective COX-2 inhibitors.

Primary outcome

The primary outcome was an ADR or HSR to the prescribed NSAID within 1 year. We chose to evaluate the fixed time frame of 1 year to allow sufficient time for patients to have a repeat visit and report an ADR/HSR. We identified ADRs and HSRs from PEAR, which contained detailed symptoms reported by patients and/or observations made by health care providers. PEAR reactions could be entered in a coded format that used a predefined list of reactions selected by providers for each drug, or a free-text format, which comprised approximately 6% of entries. For free-text reaction entries, informatician investigators (KHL, LZ) used natural language processing algorithms to automatically map reactions to a standardized form.^{11,21} For example, the free-text reaction “full body hives” was mapped to the coded reaction “hives.” All mapped free-text reactions were manually verified by another investigator (KGB).

We considered all PEAR reaction entries an ADR. We defined HSRs as the subset of ADRs that included reactions mapped to anaphylaxis, hypotension, angioedema, swelling, rhinitis, bronchospasm, asthma, wheezing, shortness of breath, hives, urticaria, itching, or rash.²² We additionally considered nonimmediate HSRs previously attributed to NSAIDs by performing key word searches of the PEAR reaction field for serum sickness, drug rash eosinophilia and systemic symptoms syndrome, erythema multiforme, acute interstitial nephritis, fixed drug eruption, erythema nodosum, Stevens-Johnson syndrome, toxic epidermal necrolysis, pneumonitis, meningitis, lichenoid drug eruptions, and leukocytoclastic vasculitis.^{6,23} Remaining known reactions were considered side effect reactions, which we grouped and sorted by frequency. “Unknown” reactions were considered separately, and could reflect that the patient and/or the provider did not know the reaction details.

Because PEAR allows for drug class entries (eg, NSAIDs) as well as specific drug entries (eg, diclofenac), we conducted a sensitivity analysis of ADR and HSR incidence by assuming that all PEAR allergy entries of “NSAID” were related to the NSAID that was prescribed. For this expanded definition, we similarly distinguished HSRs, side effects, and unknown reactions.

We used identical methods to identify the incidence of ADRs and HSRs among adult outpatients prescribed only celecoxib or meloxicam from January 1, 2004, through September 30, 2012, and who had at least 1 visit within 1 year at any PHS outpatient clinic after the prescription.

Predictor variables

Age (at the time of first NSAID prescription), gender, and race/ethnicity were identified from EHR demographic tables. We defined ADR and HSR histories using the PEAR database. We identified NSAID treatment indications (eg, rheumatoid arthritis, joint pain, chronic pain) as a coded or free-text entry into the EHR “Problem List” or presence of the relevant code(s) from the International Classification of Diseases, ninth edition (ICD-9) entered within 30 days of the NSAID prescription. All ICD-9 codes were informed by prior studies, when available (Table E2, available in this article's

Online Repository at www.jaci-inpractice.org). Patient comorbidities were identified similarly, as either on the patient's "Problem List" or presence of a relevant ICD-9 code before the NSAID prescription date. To search patients with AERD, we used key word searches of the reaction field and a previously studied informatics algorithm.²⁴ Using the NSAID electronic prescription, we created a Food and Drug Administration "maximum daily dose" for each NSAID: diclofenac 200 mg/day, indomethacin 150 mg/day, nabumetone 2000 mg/day, and piroxicam 20 mg/day.²⁵ We used the EHR "Medication List" to define medication-specific covariates, including any previous NSAID prescription (prescriptions for over-the-counter NSAIDs such as ibuprofen and naproxen, when present, were included) and concomitant medications, defined as an active EHR prescription for the medication (aspirin, opiates, or angiotensin-converting enzyme inhibitors) at the time of NSAID prescription. The classification of drugs into the opiate and angiotensin-converting enzyme inhibitor classes followed the American Hospital Formulary Service Pharmacologic-Therapeutic Classification.^{11,26}

Statistical analyses

Data are displayed as numbers with frequencies and medians with interquartile ranges. For the primary NSAID cohort, we compared binary variables using Fisher's exact test, nondichotomous categorical variables using the χ^2 test, ordinal variables using the Cochran-Armitage trend test, and continuous variables using the Wilcoxon rank sum test. To identify NSAID HSR risk factors, we created multivariable logistic regression models for the primary outcome of HSR, first using the standard HSR definition, and then using the expanded HSR definition that included NSAID class allergies.

The regression models were built using both *a priori* knowledge and imbalances between groups identified in univariable analyses. We used $P < .05$ as the screening criterion for each potential covariate not informed by prior knowledge. Our final chosen models included all variables significant at $P < .05$ in at least one of the multivariable models. We calculated odds ratios with 95% confidence intervals. P values $< .05$ were considered statistically significant. Statistical analyses were performed in SAS version 9.4 (Cary, NC). This study was approved by the Partners Institutional Review Board.

RESULTS

Incidence and phenotypes

Of 62,719 patients prescribed oral diclofenac, indomethacin, nabumetone, or piroxicam from January 1, 2004, through September 30, 2012, 1,035 (1.7%) had an ADR (Table I). ADRs included 189 patients (18.3% of ADRs; 0.3% incidence) with HSRs. HSRs included rash ($n = 72$, 38.1%), angioedema or swelling ($n = 51$, 27.0%), urticaria or hives ($n = 37$, 19.6%), itching ($n = 28$, 14.8%), shortness of breath, asthma, or wheezing ($n = 12$, 6.3%), and anaphylaxis or hypotension ($n = 10$, 5.3%). We identified only one nonimmediate HSR, serum sickness, in 1 patient. Among 801 patients who experienced side effect reactions, the most common reactions were gastrointestinal upset ($n = 543$, 67.8%), dizziness ($n = 59$, 7.4%), headaches ($n = 52$, 6.5%), mental status change ($n = 33$, 4.1%), and renal toxicity ($n = 31$, 3.9%).

Using the expanded definition of NSAID ADRs/HSRs, the incidence of NSAID ADRs was 1.8% and the incidence of NSAID HSRs remained 0.3%, or 18.6% of ADRs.

Of 32,215 patients prescribed celecoxib or meloxicam from January 1, 2004, through September 30, 2012, 429 (1.3%) had

TABLE I. Incidence of adverse drug reactions and hypersensitivity reactions to prescription NSAIDs ($n = 62,719$)

	Incidence within 1 y, n (%)
Adverse drug reactions*	1035 (1.7)
Hypersensitivity reactions†	189 (0.3)
Rash	72 (0.11)
Angioedema or swelling‡,§	51 (0.08)
Urticaria or hives§	37 (0.06)
Itching	28 (0.04)
Bronchospasm, wheezing, or shortness of breath	12 (0.02)
Anaphylaxis or hypotension	10 (0.02)
Serum sickness	1 (0.002)
Side effects ,¶	801 (1.3)
Gastrointestinal upset	543 (0.87)
Dizziness	59 (0.09)
Headache	52 (0.08)
Mental status change	33 (0.05)
Renal toxicity	31 (0.05)
Unknown	55 (0.1)

NSAID, Nonsteroidal anti-inflammatory drug.

*Using the expanded definition, ADR incidence was 1,156 of 62,719 (1.8%).

†Using the expanded definition, HSR incidence was 215 of 62,719 (0.3%). Numbers sum to >189 because providers can document more than one reaction per drug.

‡Includes 1 patient with diagnosis of chronic idiopathic urticaria/angioedema.

§Three patients had both angioedema or swelling and urticaria or hives.

||We show only the 5 most common side effect reactions.

¶Ten patients had both a hypersensitivity reaction and side effect to prescribed NSAID.

an ADR, of which 121 (28.2% of ADRs; 0.4% incidence) had an HSR (Table E3, available in this article's Online Repository at www.jaci-inpractice.org). Using the expanded ADR/HSR definition, 616 (1.9%) had an ADR, of which 163 (26.5% of ADRs; 0.5% incidence) were HSRs.

Factors associated with NSAID HSRs

In univariable analyses, patients who developed an NSAID HSR were more commonly female (Table II). Self-reported race/ethnicity was imbalanced between HSR and non-HSR groups; the frequency of Hispanic patients was lower in people experiencing an HSR than those not experiencing one (2.1% vs 5.2%). Patients with an NSAID HSR had a median of 2 more office visits the year after prescription ($P < .001$). They were more likely to have any ADR history ($P < .001$), more prior ADRs ($P < .001$), prior NSAID ADRs ($P = .03$), any HSR history ($P < .001$), more prior HSRs ($P < .001$), and prior NSAID HSRs ($P = .04$). The patients were more likely to be prescribed the NSAID for rheumatoid arthritis (3.7% vs 1.6%, $P = .03$) and joint pain (15.9% vs 10.0%, $P = .01$). They were more likely to have autoimmune disease (11.6% vs 6.1%, $P = .003$). We did not find a relationship between NSAID HSRs and atopy (20.6% vs 17.0%, $P = .21$) or chronic urticaria/angioedema (0.5% vs 0.4%, $P = .50$). One patient with an NSAID HSR was identified with AERD. Patients with an NSAID HSR were more likely to have the maximum NSAID dose prescribed (31.8% vs 25.0%, $P = .04$); patients with an HSR were more likely to have previous exposure to NSAIDs and more prior NSAID prescriptions ($P = .03$ and $P = .001$, respectively). Patients with NSAID HSRs were not more likely

TABLE II. Characteristics of patients prescribed NSAIDs who did and did not develop a hypersensitivity reaction

	All (n = 62,719)	HSR (n = 189)	No HSR (n = 62,530)	P value*
Patient characteristics				
Age, median [IQR]	52.4 [41.7, 63.2]	51.5 [42.6, 63.9]	52.4 [41.7, 63.2]	.97
Female sex	34,784 (55.5)	134 (70.9)	34,650 (55.4)	<.001
Race/ethnicity				.07
White	47,247 (75.3)	146 (77.3)	47,101 (75.3)	
Black	4,542 (7.2)	16 (8.5)	4,526 (7.2)	
Hispanic	3,279 (5.2)	4 (2.1)	3,275 (5.2)	
Asian	1,325 (2.1)	5 (2.7)	1,320 (2.1)	
Other	848 (1.4)	6 (3.2)	842 (1.4)	
Unknown	5,478 (8.7)	12 (6.4)	5,466 (8.7)	
Number of visits, median [IQR]	6 [3, 11]	8 [4, 14]	6 [3, 11]	<.001
ADR history				
Prior ADR	19,928 (31.8)	88 (46.6)	19,840 (31.7)	<.001
Number of prior ADRs				<.001
1	11,422 (18.2)	38 (20.1)	11,384 (18.2)	
2-5	7,928 (12.6)	38 (20.1)	7,890 (12.6)	
>5	578 (0.9)	12 (6.4)	566 (0.9)	
Prior NSAID ADR	1,527 (2.4)	10 (5.3)	1,517 (2.4)	.03
HSR history				
Prior HSRs	9,380 (15.0)	52 (27.5)	9,328 (14.9)	<.001
Number of prior HSRs				<.001
1	6,902 (11.0)	30 (15.9)	6,872 (11.0)	
2-5	2,434 (3.9)	18 (9.5)	2,416 (3.9)	
>5	44 (0.1)	4 (2.1)	40 (0.1)	
Prior NSAID HSR	439 (0.7)	4 (2.1)	435 (0.7)	.04
NSAID indications†				
Rheumatoid arthritis	991 (1.6)	7 (3.7)	984 (1.6)	.03
Joint pain	6,287 (10.0)	30 (15.9)	6,257 (10.0)	.01
Chronic pain	305 (0.5)	3 (1.6)	302 (0.5)	.07
Osteoarthritis	4,547 (7.3)	20 (10.6)	4,527 (7.2)	.09
Gout	3,013 (4.8)	7 (3.7)	3,006 (4.8)	.61
Pseudogout	83 (0.1)	0 (0)	83 (0.1)	1.00
Back pain	7,194 (11.5)	29 (15.3)	7,165 (11.5)	.11
Myocarditis/pericarditis	162 (0.3)	0 (0)	162 (0.3)	1.00
Abdominal pain	1,081 (1.7)	3 (1.6)	1,078 (1.7)	1.00
Dysmenorrhea	92 (0.2)	0 (0)	92 (0.2)	1.00
Headache‡	2,493 (4.0)	12 (6.4)	2,481 (4.0)	.09
Acute pain	118 (0.2)	0 (0)	118 (0.2)	1.00
General comorbidities§				
Autoimmune disease	3,828 (6.1)	22 (11.6)	3,806 (6.1)	.003
Atopic conditions	10,669 (17.0)	39 (20.6)	10,630 (17.0)	.21
Chronic urticaria/angioedema	227 (0.4)	1 (0.5)	226 (0.4)	.50
Malignancy¶	5,821 (9.3)	14 (7.4)	5,807 (9.3)	.45
Cardiac conditions	3,521 (5.6)	9 (4.8)	3,512 (5.6)	.75
Cerebrovascular disease	698 (1.1)	3 (1.6)	695 (1.1)	.47
Chronic renal impairment	1,027 (1.6)	2 (1.1)	1,025 (1.6)	.77
NSAID characteristics				
Maximum dose prescribed	15,666 (25.0)	60 (31.8)	15,606 (25.0)	.04
Prior NSAID prescription	26,933 (42.9)	96 (50.8)	26,837 (42.9)	.03
Number of prior prescriptions for NSAIDs				.001
1	18,089 (28.8)	56 (29.6)	18,033 (28.8)	
2-5	8,703 (13.9)	38 (20.1)	8,665 (13.9)	
>5	141 (0.2)	2 (1.1)	139 (0.2)	
Concomitant medications#				

(continued)

TABLE II. (Continued)

	All (n = 62,719)	HSR (n = 189)	No HSR (n = 62,530)	P value*
Aspirin	10,854 (17.3)	35 (18.5)	10,819 (17.3)	.63
Opiate	10,050 (16.0)	37 (19.6)	10,013 (16.0)	.20
Angiotensin converting enzyme inhibitor	10,923 (17.4)	34 (18.0)	10,889 (17.4)	.85

ADR, Adverse drug reaction; EHR, electronic health record; HSR, hypersensitivity reaction; ICD-9, the International Classification of Diseases, ninth edition; IQR, interquartile range; NSAID, nonsteroidal anti-inflammatory drugs.

* χ^2 test, Fisher's exact test, Cochran-Armitage trend test, or Wilcoxon rank sum test, as indicated.

†Problem List entry or ICD-9 code billed within 30 d of NSAID prescription.

‡Includes migraine, tension, cluster, post-traumatic, and other (see Table E1 in this article's Online Repository at www.jaci-inpractice.org).

§Problem List entry or ICD-9 code billed at any time before NSAID prescription.

||Includes atopic dermatitis, allergic asthma, and allergic rhinitis (see Table E1 in this article's Online Repository at www.jaci-inpractice.org).

¶Excluding nonmelanomatous skin cancer (see Table E1 in this article's Online Repository at www.jaci-inpractice.org).

#Active EHR prescription at the time of NSAID prescription.

TABLE III. Summary of multivariable analyses of hypersensitivity reactions to NSAIDs

Factors associated with increased odds of HSR*	Standard HSR definition		Expanded HSR definition	
	Odds ratio [95% CI]	P value†	Odds ratio [95% CI]	P value†
Prior drug HSR history	1.8 [1.3, 2.5]	<.001	1.8 [1.4, 2.5]	<.001
Female sex	1.8 [1.3, 2.4]	<.001	1.7 [1.2, 2.2]	<.001
Autoimmune disease‡	1.7 [1.1, 2.7]	.02	1.6 [1.1, 2.5]	.03
Prescribing the maximum standing NSAID dose	1.5 [1.1, 2.0]	.01	1.3 [1.0, 1.8]	.07

HSR, Hypersensitivity reaction; ICD-9, the International Classification of Diseases, ninth edition; NSAID, nonsteroidal anti-inflammatory drug.

*Models control for number of patient visits, for standard HSR definition odds ratio 1.0 [95% CI 1.0-1.0], $P = .02$, and for the expanded HSR definition odds ratio 1.0 [95% CI 1.0-1.0], $P = .004$.

†Wald χ^2 .

‡Patient comorbidity, Problem List entry, or ICD-9 code billed at any time before NSAID prescription.

to have concomitant aspirin, opiate, or angiotensin-converting enzyme inhibitor prescribed.

In multivariable logistic regression analysis, we identified that patients with prior drug HSR history (odds ratio [OR] 1.8 [95% CI 1.3, 2.5]), female sex (OR 1.8 [95% CI 1.3, 2.4]), autoimmune disease (OR 1.7 [95% CI 1.1, 2.7]), and prescribed the maximum standing NSAID dose (OR 1.5 [95% CI 1.1, 2.0], Table III) have an increased odds of NSAID HSR. Using the expanded HSR definition led to a similar multivariable model with slightly lower OR estimates for female sex and autoimmune disease, and approximately the same OR estimate for prior drug HSR history. In the expanded model, prescribing the maximum standing NSAID dose lost statistical significance (OR 1.3 [95% CI 1.0, 1.8], $P = .07$).

DISCUSSION

In this study, we used a large amount of EHR data to identify the reported incidence, reaction types, and risk factors for HSRs to 4 prescription-only NSAIDs. We found that although most patients tolerate their NSAID prescription, at least 1.7% of patients taking NSAIDs reported an ADR. We used informatics techniques to identify that about 1 in 5 NSAID ADRs was likely an HSR. Finally, we identified risk factors for NSAID HSRs that can be used to guide patient counseling, including prior drug HSR history, female sex, autoimmune disease, and prescribing the maximum NSAID dose.

Our observed 1-year incidence of ADRs was 1.7%, and using an expanded definition, ADR incidence was 1.8%. This estimate falls within the range of previously reported estimates.^{10,12} We found NSAID side effect reactions, including some potentially

mild (ie, gastrointestinal complaints, dizziness, headache) and some potentially severe (eg, nephrotoxicity) that are similar to prior data.^{1,12,25} Patients prescribed only COX-2 inhibitors had a lower overall 1-year ADR incidence using the standard definition (1.3%), whereas using the expanded definition, incidence was similar (1.9%). For these patients, HSRs comprised a greater proportion of the ADRs (28.2% using the standard definition and 26.5% using the expanded definition). Although not evaluated explicitly, this finding might be explained by underlying differences in patients prescribed only COX-2 inhibitors (eg, patients who have chronic urticaria/angioedema). Many patients who suffer NSAID ADRs and/or HSRs have diagnoses that warrant continued NSAID use, which poses a barrier to optimal medical treatment or presents a conflict with maintaining patient safety. Indeed, NSAIDs are identified as the culprit drug responsible for 1 in 10 ADRs that require hospital admission.^{2,3,5}

In this study, we identified that about 1 in 5 NSAID ADRs was an HSR. Because NSAID use is ubiquitous and increasing both nationally and internationally, awareness of NSAID HSRs is clinically important. Although this study is the first to define the proportion of NSAID ADRs that are HSRs, the composition is similar to prior reported estimates of the general contribution of drug hypersensitivity to adverse drug events.²⁷ Although many patients with HSRs to any NSAID must avoid the entire class of NSAIDs, some patients have an HSR to a specific (ie, singular) NSAID or group of NSAIDs with a shared chemical structure.¹³ The current schema for categorizing NSAID HSRs includes 4 types of pseudoallergic reactions (elicited by the enzymatic activity of the cyclooxygenase enzyme) and 2 allergic reactions (presumed mediated by IgE).^{13,28} Pseudoallergic reactions specifically include asthma and rhinosinusitis (type 1), NSAID-

induced urticaria/angioedema in patients with chronic urticaria (type 2), NSAID-induced urticaria/angioedema in otherwise asymptomatic patients (type 3), and blended reactions involving mixed respiratory and cutaneous findings (type 4). Allergic reactions include reactions to a single NSAID or group of NSAIDs with similar chemical structure. Among allergic reactions, type 5 is urticaria or angioedema and type 6 is anaphylaxis; however, type 5 and type 6 reactions are thought to be due to the same IgE mechanism with different reaction severity.^{13,28,29} The systematic evaluation and classification of patients with NSAID HSRs can help determine future viability of NSAIDs. However, because of the complexity involved with classification of NSAID HSRs, patients who require aspirin or NSAID treatment who have a prior NSAID HSR may benefit from evaluation by an allergy specialist.^{6,30-34}

We identified female sex as a risk factor for NSAID HSRs, which is consistent with previous EHR-based reports.^{10,19,35} Prior drug allergy data have generally demonstrated that higher doses and longer courses increase risk of HSRs.^{6,10,35} We similarly identified prescribing the maximum NSAID dose was a risk factor for an NSAID HSR. This observed "dose responsiveness" suggests that many of the HSRs were likely pseudoallergic rather than IgE mediated. Consistent with this hypothesis, we found that atopy, described to be more common in IgE-mediated NSAID allergy, was not a significant predictor in this cohort.¹⁸ One prior study using 11 ICD-9 HSR codes in a US Medicaid dataset found that rheumatoid arthritis increased odds of NSAID HSR.¹⁹ We similarly found increased frequency of HSR with rheumatoid arthritis in univariable analysis, and autoimmune disease was associated with a 60% to 70% increased odds of NSAID HSRs in multivariable analysis. Defining the relationship between NSAID HSRs and autoimmune disease is an important area for future prospective study.

Despite the clinical experience of allergists who evaluate patients with NSAID HSRs, we did not find chronic urticaria/angioedema to increase odds of HSR. This could be due to variable clinical documentation of chronic urticaria/angioedema in EHRs or provider awareness that NSAIDs are relatively contraindicated in patients with chronic urticaria/angioedema. Although a validated, ICD-9 coding algorithm exists to identify chronic idiopathic urticaria using EHRs, we found only 227 patients (0.4%) with the disease, and only 1 patient with chronic urticaria/angioedema who developed an NSAID HSR. Although there is a well-defined relationship between nasal and respiratory HSR symptoms and AERD, we found only one case of AERD in this cohort. It is possible that patients with AERD were appropriately not prescribed NSAIDs and therefore not represented in this cohort.²⁴ Further studies that assess NSAID prescription patterns among patients with chronic urticaria/angioedema and AERD are required to understand these findings. Acute pain, although a significant predictor in the prior claims-based study,¹⁹ was not a predictor in this study; of 118 patients identified in the cohort with acute pain, none developed an HSR.

There are several limitations to this analysis. First, the allergy data we used in this study are not validated; drug and reaction data can be patient reported and/or clinician observed. The data vary in quality and many health care team members lack drug allergy knowledge to appropriately enter allergy assessments.³⁶⁻³⁸ Attribution of an ADR or HSR may not have been correctly identified, and given the large-scale, retrospective nature of this

study, no formal causality assessment (eg, Naranjo ADR probability scale or World Health Organization causality criteria)³⁹ would have been feasible. However, use of usual clinical care allergy data has benefits; regardless of whether the association between the drug and reaction is true, the patient's EHR report of NSAID allergy will impact future prescribing of all NSAIDs, including aspirin.^{40,41} We chose to evaluate the allergy record at one fixed time period after prescription (1 year) because this would allow sufficient time for a patient to visit a doctor in our health care system and report an ADR to NSAIDs. However, we still may have missed minor reactions that patients did not remember at their visit or reactions that patients discounted as not important. Because Partners HealthCare is an integrated yet open health care system, we were also limited by not knowing patients' complete medications, which could include outside hospital prescriptions and over-the-counter medications, including other NSAIDs. Although we chose to study prescription-only NSAIDs and primarily report ADRs/HSRs to the identically prescribed NSAID (ie, the standard definition and analysis) to minimize the impact of this issue, all NSAIDs may not have similar propensities to cause ADRs/HSRs.^{19,42} Incidence of ADRs and HSRs may have been higher if we were able to evaluate aspirin, ibuprofen, and/or naproxen, the NSAIDs with the highest prevalence of reported allergy in both the US and the PEAR database.¹¹ Finally, we cannot exclude the possibility of selection bias toward patients who tolerate NSAIDs, because 43% of patients had prior NSAIDs prescribed with many tolerated, and 17% of cohort patients were taking and presumably tolerating aspirin.

By examining a large retrospective cohort of outpatients, we find that the 1-year incidence of ADRs to prescription NSAIDs is 1.7% to 1.8%; about 1 in 5 ADRs was an HSR. Patients prescribed COX-2 inhibitors only had a similar incidence of ADRs (1.3%-1.9%), although a greater proportion of ADRs were HSRs. Our data identify NSAID HSR risk factors, including prior drug HSR history, female sex, autoimmune disease, and prescribing the maximum NSAID dose. Clinician awareness of NSAID hypersensitivity in patients with these risk factors could guide patient counseling and safe prescribing practices.

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ONLINE REPOSITORY

TABLE E1. Cross-sectional analysis of NSAID adverse drug reactions (ADRs) in the Partners Enterprise Allergy Repository from 2003 through 2013 (n = 2,730,250)

NSAID	Patients with ADR, n (%)
Aspirin*	40,557 (1.49)
Ibuprofen*	17,092 (0.63)
Naproxen*	9,694 (0.36)
Celecoxib†	4,285 (0.16)
Indomethacin	2,725 (0.10)
Rofecoxib‡	2,551 (0.09)
Ketorolac§	2,147 (0.08)
Diclofenac	1,673 (0.06)
Nabumetone	1,147 (0.04)
Piroxicam	1,028 (0.04)
Meloxicam†	640 (0.02)
NSAIDs (entered as class)	22,260 (0.82)

NSAIDs included in the primary analysis.

NSAID, Nonsteroidal anti-inflammatory drug.

*Excluded due to availability over-the-counter. Prescriptions for over-the-counter NSAIDs are written for a nonrandom patient subset.

†Considered separately due to a distinct mechanism (selective cyclooxygenase 2 inhibitor).

‡Excluded because withdrawn from market in 2004.

§Excluded because the predominant route was not oral (ophthalmologic use).

TABLE E2. Billing codes and algorithms used for patient clinical characteristics

Variable definition*		Available references
Indications		
Rheumatoid arthritis	714.xx†, 720.0	E1, E2
Joint pain	719.4x	
Chronic pain	338.2x, 338.4	E3
Osteoarthritis	715.xx, 716.xx	E4-E6
Gout	274.xx	E7
Pseudogout/chondrocalcinosis	275.49, 712.1-712.39	E8
Back pain	721.xx, 722.xx, 724.02, 724.2, 724.3, 724.4, 724.5, 739.x, 847.2, 847.9	E9, E10
Myocarditis/pericarditis	072.xx, 079.9x, 420.xx, 422.xx, 429.0	E11
Abdominal pain	789.0x	E12
Dysmenorrhea	306.52, 625.3	E13
Acute pain	338.1x	
Headache‡	307.81, 339.xx, 346.xx, 784.0	E14
Comorbidities		
Autoimmune disease§	242.0x, 245.2, 250.x1, 250.x3, 286.5x, 358.0x, 555.x, 556.x, 579.0, 696.0, 696.1, 710.0, 710.2, 714.0, 714.1, 714.2, 714.3x	E15
Atopic conditions	477.xx, 493.xx, 691.xx, 692.xx	E16-E18
Chronic urticaria/angioedema	708.1, 708.8, 708.9	E19
Aspirin-exacerbated respiratory disease	Key word search, informatics algorithm	E20
Malignancy¶	140-149.9, 150-159.9, 160-164.9, 170-172.9, 174-175.9, 180.x, 182-186.9, 187.3, 187.4, 187.9, 188-189.9, 190-197.8, 199.x, 235.x, 236.1, 236.2, 236.4, 236.5, 236.6, 236.7, 236.91, 237.xx, 238.1, 238.2, 238.8, 238.9, 239.xx	E21
Cardiac conditions#	410.9x, 414.0x, 428.xx	
Cerebrovascular disease	431, 433.x1, 434.xx, 436, V12.54	E22
Chronic renal impairment	403.11, 403.91, 404.12, 404.13, 404.92, 404.93, 585.xx, 586, 587	E23

ICD-9, International Classification of Diseases, ninth edition; NSAID, nonsteroidal anti-inflammatory drug.

*Definitions using billing codes required the presence of 2 or more ICD-9 codes within 30 days of NSAID prescription (indications) or at any time before NSAID prescription (comorbidities).

†“x” and “xx” denote any integer from 1 through 9.

‡Includes migraine, tension, cluster, post-traumatic, and other.

§Includes antiphospholipid syndrome, celiac disease, Crohn’s disease, ulcerative colitis, type 1 diabetes, systemic lupus erythematosus, Sjogren syndrome, rheumatoid arthritis, psoriasis, myasthenia gravis, Hashimoto’s thyroiditis, and Graves’ disease.

||Includes atopic dermatitis, allergic asthma, and allergic rhinitis.

¶Excluding nonmelanomatous skin cancer.

#Includes coronary artery disease, myocardial infarction, and congestive heart failure.

TABLE E3. Incidence of adverse and hypersensitivity reactions to celecoxib or meloxicam (n = 32,215)

	Incidence within 1 y n (%)
Adverse drug reactions*	429 (1.3)
Hypersensitivity reactions†	121 (0.4)
Rash	62 (0.19)
Urticaria or hives‡	22 (0.07)
Itching	20 (0.06)
Angioedema or swelling‡,§	20 (0.06)
Bronchospasm, wheezing, or shortness of breath	8 (0.02)
Anaphylaxis or hypotension	5 (0.02)
Side effects ,¶	269 (0.8)
Gastrointestinal upset	175 (0.54)
Renal toxicity	15 (0.05)
Mental status change	13 (0.04)
Gastrointestinal bleeding	13 (0.04)
Dizziness	12 (0.04)
Unknown	47 (0.15)

NSAID, Nonsteroidal anti-inflammatory drug.

*Using the expanded definition, ADR incidence was 616 of 32,215 (1.9%).

†Using the expanded definition, HSR incidence was 163 of 32,215 (0.5%). Numbers sum to >121 because providers can document more than one reaction per drug.

‡One patient had both angioedema or swelling and urticaria/hives.

§Includes 1 patient with diagnosis of chronic idiopathic urticaria/angioedema.

||We show only the 5 most common side effect reactions.

¶Eight patients had both a hypersensitivity reaction and side effect to prescribed NSAID.

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