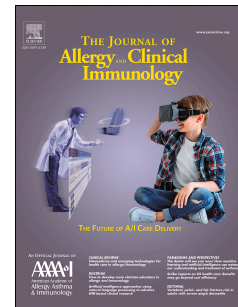


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Impact of reported NSAID “allergies” on opioid use disorder in back pain

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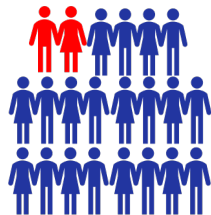
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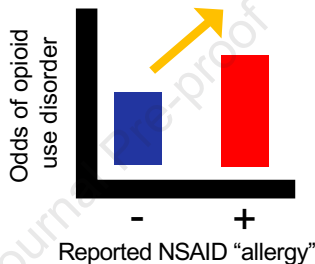


Impact of reported NSAID “allergies” on opioid use disorder in back pain



Cohort of adults with chronic back pain (n=47,114)

7.7% with reported NSAID “allergy” (n=3,620)



Increased odds of opioid use disorder in patients with reported NSAID “allergy”

NSAID, non-steroidal anti-inflammatory drug

Impact of reported NSAID “allergies” on opioid use disorder in back pain

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ABSTRACT

Background: It is crucial to identify patients at highest risk for opioid use disorder (OUD) and to address challenges in reducing opioid use. Reported non-steroidal anti-inflammatory drug (NSAID) allergies may predispose to use of stronger pain medications and potentially to OUD.

Objective: Investigate the clinical impact of reported NSAID allergy on OUD in patients with chronic back pain.

Methods: We conducted a retrospective study of adults receiving care at a tertiary healthcare system from 1/1/2013-12/31/2018. Back pain and OUD were identified using administrative data algorithms. We used propensity score matching and logistic regression to estimate the impact of self-reported NSAID adverse drug reactions (ADRs) on risk of OUD, adjusting for other relevant clinical information.

Results: Of 47,114 patients with chronic back pain, 3,620 (7.7%) had a reported NSAID ADR. In an adjusted propensity score matched analysis, patients with NSAID ADRs had higher odds (OR 1.34 [95% CI 1.07-1.67]) of developing OUD as compared to those without NSAID ADRs. Additional risk factors for OUD included younger age, male sex, Medicaid insurance, Medicare insurance, higher number of inpatient and outpatient visits in the prior year, and co-morbid anxiety and depression. Patients with listed NSAID ADRs also had higher odds of a documented opioid prescription during the study period (OR 1.22 [95% CI 1.11-1.34]).

Conclusion: Adults with chronic back pain and reported NSAID ADRs are at higher risk of developing OUD and receiving opioid analgesics, even after accounting for co-morbidities and health care utilization. Allergy evaluation is critical for potential de-labeling of patients with reported NSAID allergies and chronic pain.

Clinical Implication:

Patients with chronic back pain and self-reported NSAID allergies are at increased risk for developing OUD and should be referred to Allergy specialists for targeted evaluation and consideration of drug challenge to reduce the risk of OUD.

Capsule Summary:

Reported NSAID allergy represents a risk factor for OUD in patients with chronic back pain. There may be an important role for Allergy specialists in the multi-disciplinary care, evaluation, and de-labeling of patients with pain and with reported NSAID allergies.

Key words:

Aspirin; non-steroidal anti-inflammatory drug (NSAID); hypersensitivity; drug allergy; adverse drug reaction; opioid use disorder; analgesics; outpatient; utilization; electronic health record

Abbreviations:

ADR – adverse drug reaction

CI – confidence interval

COX – cyclooxygenase

EHR – electronic health record

ICD – International Classification of Diseases

116 NSAID - non-steroidal anti-inflammatory drug

117 OR – odds ratio

118 OUD – opioid use disorder

119 SD – standard deviation

120 PHS – Partners Healthcare System

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INTRODUCTION

The opioid epidemic remains a pressing public health problem, with opioid-related overdoses claiming over 47,000 lives in the United States in 2017 (1, 2). Opioid use presents serious risks, with higher dosages and prescription lengths associated with long-term opioid use, incident opioid use disorder (OUD), and increased overdose risk (3-6). Opioid prescription rates remain astonishingly high (7, 8), primarily due to high rates of opioid use for non-cancer chronic musculoskeletal pain (9, 10). A large body of work continues to demonstrate that opioids are not superior to non-opioids for improving pain-related function in patients with chronic back pain, and are actually associated with higher adverse medication-related symptoms (11, 12). It is thus imperative to minimize unnecessary opioid exposures and to identify and address challenges in reducing opioid use among current opioid users with non-cancer chronic conditions.

Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly prescribed for treatment of acute and chronic pain (13), but their therapeutic use is limited by reported allergies. Colloquially, these “allergies” reflect adverse drug reactions (ADRs) which encompass both known side effects (e.g. gastrointestinal upset, bleeding) and true allergic hypersensitivity reactions. NSAID ADRs are the second most commonly reported class of drug allergies, surpassed only by antibiotic allergies (14). However, it is estimated that only 20% of patients with self-reported NSAID ADRs actually have reactions consistent with NSAID hypersensitivity (15). Furthermore, even true hypersensitivity reactions to NSAIDs are generally not caused by immunologic mechanisms, but rather by pharmacologic inhibition of COX-1 (16). In fact, over

95% of patients with true NSAID hypersensitivity can safely receive celecoxib, a selective COX-2 inhibitor (17-20).

Allergy over-reporting and lack of further investigation by an Allergy specialist may lead to unnecessary avoidance of non-selective NSAIDs and COX-2 inhibitors, and both pain undermanagement and increased utilization of opioids. One recent study suggested that starting and stopping NSAIDs were both associated with higher odds of increased alternative analgesic use, including opioids, in patients with chronic kidney disease (21). Moreover, inclusion of NSAIDs and celecoxib in the post-operative setting following ambulatory surgery has been found to decrease the need for rescue analgesics and improve quality of recovery and patient satisfaction (22). Notably, no studies have previously examined the impact of non-antibiotic drug ADR reporting on drug utilization patterns and outcomes such as OUD, which have important implications for patient care and safety.

METHODS

Data sources

We performed a retrospective cohort study using electronic health record (EHR) data available within the Partners HealthCare System (PHS), an integrated health care system in Boston, Massachusetts that includes community and specialty hospitals. Patient sociodemographic information, clinical characteristics, and medication information were collected using the Partners Research Patient Data Registry database, which contains clinical and administrative information on millions of patients seen within the PHS. Allergy information was obtained from the EHR and Partners Enterprise Allergy Repository, a database of allergy and adverse effect information shared across the entire PHS network (23, 24).

Study cohort

The study cohort was comprised of patients 18-65 years old on 1/1/2013 with at least two International Classification of Diseases (ICD)-9 or ICD-10 diagnosis codes for back pain, including at least one outpatient code, prior to 1/1/2013 (25-27) (see Table E1 in this article's Online Repository). We restricted our cohort to younger adults in order to most efficiently increase the prevalence of our primary outcome (OUD) in the study population, and because the clinical management and prescribing patterns for older adults can differ from that of younger patients (28). Patients were required to have at least one outpatient visit every two years during the study period, to ensure selection of a cohort of patients receiving active care at PHS

institutions. The study period started on 1/1/2013 and ended on 12/31/2018 or date of death, whichever came first. Patients with workers' compensation in the year prior to study entry (2012) were excluded as prior studies have shown socioeconomic and clinical characteristics and prescription dispensing patterns to be different between patients receiving and not receiving workers' compensation (29, 30).

NSAID "allergy" exposure

We determined exposure status prior to study entry. The presence of any self-reported adverse reaction to aspirin or other NSAIDs (including COX-2 inhibitors) in the Allergy module of the EHR was considered positive for a reported "allergy." Allergy entries were required to be listed as active prior to the start of the study period. We chose to include all prior available allergy data for each subject in order to increase sensitivity and the chance that individuals with allergy were correctly classified. Those with no listing of any NSAID reaction ever in the EHR prior to 1/1/2013 were considered negative for the exposure and comprised the comparator group. Patients with allergy entries for only topical NSAIDs, salicylates, or 5-acetylacetic acid derivatives (e.g. sulfasalazine, mesalamine) were excluded, as some medical providers may consider these cross-reactive with oral NSAIDs, while others do not. Patients with their first NSAID allergy documented during the study period were also excluded, to ensure that presence of NSAID allergy preceded diagnosis of OUD. Individual allergy entries underwent keyword search or manual review to identify frequencies of the specific implicated drugs and reaction characteristics.

OUD outcomes and validation

Based on published algorithms (31-33), patients with OUD were identified if they had two or more ICD-9 or ICD-10 codes for opioid abuse or opioid dependence (34-36) during the observation period (see Table E1 in this article's Online Repository). We chose to require at least two ICD codes in order to minimize outcome misclassification. As this algorithm had not previously been validated, we performed a validation by randomly selecting 100 patients identified by this algorithm for manual chart review. We found that 90% in our study were correctly identified as having opioid abuse or dependence. The remaining 10% represented patients with chronic pain (including malignancy-related pain) managed with chronic opioid therapy but without evidence of opioid misuse or abuse. Patients with two or more ICD codes for OUD prior to the start of the study were excluded, in order to identify incident OUD. Analgesic, including opioid (see Table E2 in this article's Online Repository), prescription information was also obtained from the EHR and counted as present if ever listed in the patient's medication list during the study period.

Covariates

Covariates including age, sex, race, ethnicity, and insurance information were collected from the EHR prior to study start. Co-morbidities were identified if the patient had two or more relevant ICD-9 or ICD-10 diagnoses or problem list codes previously documented in the chart (15). All ICD-9 and ICD-10 codes for co-morbidities were based on prior studies, when available. Information regarding the number of unique reported NSAID allergen entries and drug reaction information was also collected.

Statistical Analysis

Summary statistics were calculated as counts with percentages for categorical variables, and means with standard deviation (SD) for normally distributed data or median with interquartiles for non-normally distributed data. Categorical variables were compared using a chi-square test, and continuous variables compared using a Students t-test or Wilcoxon rank sum test as indicated. Two sets of analyses were performed, one with the entire cohort and the other using a propensity score matched sample.

To address differences in baseline characteristics between groups, we used propensity score matching techniques to minimize the effect of confounding in our study. Specifically, we built a logistic regression model to generate propensity scores to estimate the probability of having the exposure (a reported NSAID allergy) based on patient baseline characteristics, including demographic variables, health care utilization patterns in the year prior to study entry, and co-morbidities. The covariates in the propensity score model included all baseline covariates with the exception of chronic idiopathic urticaria, which is a known predictor of NSAID-induced reactions. Subjects with reported NSAID allergies were then matched in a 1:4 ratio to patients without any reported allergies using greedy nearest-neighbor propensity score matching. In this approach, a propensity score is first calculated for each patient with a reported drug allergy. This score is then matched to the four patients without reported NSAID allergies who have propensity scores closest to that value. The balance of covariates between propensity score matched groups was assessed by calculating the standardized differences and considered well-matched if the standardized mean difference was <0.1 .

To identify OUD risk factors, we built multivariable logistic regression models using *a priori* knowledge and covariates identified as significant with $p < 0.05$ in univariable analyses. We calculated odds ratios (ORs) with 95% confidence intervals (CIs) and p -values < 0.05 were considered statistically significant. All statistical analyses were performed using SAS software, version 9.4 (Cary, NC). This study was approved by the PHS Institutional Review Board.

RESULTS

Clinical characteristics

We identified a cohort of 47,114 patients with chronic back pain receiving care at PHS institutions between January 1, 2013 and December 31, 2018. Of these, 3,620 (7.7%) individuals had a total of 5,187 active aspirin or NSAID adverse reactions listed in the Allergy module of the EHR prior to study entry. In the entire cohort, all measured baseline co-morbidities were higher in patients with reported NSAID allergies, with the exception of malignancy (excluding skin malignancy) (Table 1). Among patients with NSAID allergies, 35.8% had at least one encounter ever documented with an Allergist within the PHS, compared to 25.8% of those without NSAID allergies ($p < 0.0001$).

The 1:4 propensity score matched sample included a total of 18,100 patients. The majority of patients were female (75.9%) and white (70.3%), with a mean age of 52 years [SD 10]. Baseline characteristics were well balanced between matched groups (Table 1).

NSAID reaction characteristics

Among 5,187 recorded NSAID allergy entries in the cohort, the most commonly implicated NSAIDs were aspirin (28.7%), ibuprofen (16.7%) and naproxen (11.0%). 1,116 (21.5%) entries reported an allergy to “NSAIDs” as a class (see Table E3 in this article’s Online Repository). Based on the recorded symptoms of NSAID-induced reactions, only 39.0% of subjects reported NSAID reactions consistent with hypersensitivity-type reactions (e.g. rash or bronchospasm), while 45.0% reported side effects (e.g. gastrointestinal upset) and 16.0% had “unknown” or “other” reactions (Table 2).

The effect of NSAID allergy and other predictors of OUD

The association between presence of a reported NSAID allergy and OUD was slightly higher in the entire cohort (unadjusted OR 1.60 [95% CI 1.31, 1.95], $p < 0.0001$) compared to the propensity score matched sample (OR 1.38 [95% CI 1.11, 1.71], $p = 0.01$). The association was attenuated after adjusting for potential confounders in the multivariable logistic regression model using the entire cohort (adjusted OR 1.37 [95% CI 1.12, 1.69], $p = 0.003$), but remained at a similar level for the propensity score matched sample (adjusted OR 1.34 [95% CI 1.07, 1.67], $p = 0.01$) (Figure 1). Male sex, Medicaid, Medicare or dual insurance (versus private insurance), higher number of inpatient and outpatient encounters in the prior year, and co-morbid asthma, anxiety and depression were associated with higher risk of OUD (Table 3). In a stratified

analysis of subjects without anxiety or depression, NSAID allergy remained a significant predictor of OUD (see Table E4 in this article's Online Repository). Protective factors included older age, black (vs white) race, renal insufficiency and allergic rhinitis.

Analgesic use patterns

Patients with reported NSAID allergies were more likely to have an alternative analgesic prescription, including opioids (OR 1.22 [95% CI 1.11,1.34]), gabapentin (OR 1.20 [95% CI 1.11,1.30]), pregabalin (OR 1.48 [95% CI 1.27,1.71]) and amitriptyline (OR 1.28 [95% CI 1.13,1.46]), listed in the chart during the study period than those without reported allergies in the propensity score matched sample. We did not find a statistically significant difference in celecoxib or nortriptyline prescriptions between patients with or without reported NSAID allergies (OR 1.16 [95% CI 0.99,1.34] and OR 1.10 [95% CI 0.96,1.27], respectively). Only 810/14,480 (5.6%) patients without NSAID allergies received celecoxib during the study period, as compared to 232/3,620 (6.4%) patients with reported NSAID allergies.

DISCUSSION

Using EHR data from a large integrated health care system in the United States, we found patients with chronic back pain and reported NSAID allergies to be at increased risk for developing OUD. This association remained even after accounting for differences in outpatient

healthcare utilization and co-morbidities. Moreover, patients with reported NSAID ADRs were more likely to receive several other alternative analgesics, including opioids, and only a minority of patients had reactions consistent with drug hypersensitivity by history. While over one third of patients with reported NSAID ADRs had previously been evaluated by an Allergist, we were unable to determine how many encounters were specifically for NSAID allergy evaluation or a separate non-NSAID allergy-related issue, as manual medical record review was not feasible for such a large cohort. Taken together, these results indicate a need for careful, directed evaluation and clarification of reported NSAID “allergies,” in order to further de-labeling efforts and identify patients for which non-selective NSAIDs are an absolute contraindication, versus those with side effects or idiosyncratic reactions which may not necessarily preclude use of this class of medication.

While our EHR system is limited to evaluation of prescribed or historical medications entered by a physician, rather than claims or medication fill data, the relationships between reported drug allergies and prescription patterns remain critically important and understudied outside of antibiotic allergies. Prior work has clearly demonstrated that beta-lactam allergy labels directly impact antimicrobial stewardship by leading to use of broader spectrum, less effective antimicrobials and are associated with antimicrobial resistance, higher costs, and delays in care (37). Our findings suggest that for patients with chronic back pain, having a reported NSAID allergy is associated with higher risk of receiving other analgesic medications, including opioids. Many NSAIDs are available over-the-counter and less costly than alternative drugs such as opioids or tricyclic anti-depressants. Additional work is needed to further investigate the impact

of aspirin and NSAID allergy labels on individual and societal costs, as well as on patient safety and outcomes.

The diagnosis of OUD is made clinically, and recent public health efforts have focused on decreasing both the quantity and doses of opioids prescribed to curb rates of incident OUD, as well as identifying and treating patients with previously diagnosed OUD (38). Strikingly, 39% of heroin injectors who had used within the prior four months and over 80% of young heroin users under 25 years old reported misuse of prescription opioids *prior* to heroin use (39, 40). Allergy evaluation of patients with chronic pain and reported NSAID allergies would therefore ideally occur as early as possible in order to help prevent unnecessary opioid prescriptions and potentially, the development of OUD. However, even for patients with previously diagnosed OUD who have undergone treatment with detoxification, relapse rates are high and range from 32-88% after 12-36 months (41). The prevalence of stable abstinence from opioid use after 10-30 years is less than 30% (42). Management of chronic and acute (e.g. peri-operative) pain can be particularly challenging in this population, as poorly controlled pain can lead to cravings and relapse (43). Allergy evaluation and NSAID allergy de-labeling may thus prove a critical part of the ongoing multi-disciplinary care of patients with chronic pain and inflammatory conditions for which NSAIDs are first-line but contraindicated due to presumed allergy, and those with previously diagnosed OUD.

Surprisingly, overall use of celecoxib was low in this population and we did not find a statistically significant difference in documented celecoxib prescriptions between patients with and without reported NSAID allergies. This suggests that COX-2 inhibitors are underutilized,

particularly for patients with reported hypersensitivity to non-selective NSAIDs, despite data indicating good tolerability in this population (17, 20).

Consistent with the published literature, we found younger age, male sex, and co-morbid anxiety and depression to be associated with increased odds of OUD in our study population (44). Others have previously found unemployment, no insurance, and Medicaid insurance to predict OUD in large population-based studies (45), and that opioid prescriptions are frequent (>40%) in the Medicare under age 65 group (46). As such, the strong link of Medicare and Medicaid insurance with OUD in our study was not surprising. Renal disease and allergic rhinitis were associated with reduced odds of OUD, while asthma was associated with increased odds of OUD. While the role of co-morbid allergic diseases in opioid use disorder is not clear, the prevalence of asthma in patients with OUD has previously been found to be higher than the national prevalence of asthma (47, 48). The associations found in our study clearly highlight the need for future, prospective studies to more definitively address the role of atopy and reported NSAID allergies on prescribing patterns and development of opioid use disorder.

The findings presented here are subject to several limitations. First, due to the nature of the observational, retrospective analysis employed in our study design, only associations and not causation may be drawn from our findings. Second, our study cohort may not be generalizable to all patients with chronic back pain, as we excluded patients with worker's compensation and those over 65 years old. However, prior research shows that younger individuals are at highest risk of OUD (44) and given the thousands of patients included in the study, our findings remain informative and relevant. Third, there were many differences in characteristics between subjects

with and without reported NSAID allergies at baseline. While propensity score matching balances measured confounders, unmeasured confounders remain a limitation of all non-randomized studies. Unmeasured confounders relevant to this study may include cumulative prior prescription and over-the-counter NSAID use, other conditions predisposing to or precluding NSAID or opioid use, co-morbid non-opioid substance use disorders associated with chronic pain, and socioeconomic factors (e.g. employment status) that may affect access to care. Such factors can be challenging to systematically capture from large datasets involving EHR-data, but are critically important to recognize. Finally, it is possible that some OUD cases may have represented prevalent rather than incident cases due to clinician coding practices. This problem is intrinsic to use of EHR data for the study of many clinical diagnoses, which could have occurred in the past but are only entered when a patient presents to seek care. To address the specific timing of relationships between reported NSAID allergies and OUD diagnoses, we specifically designed our study to require documentation of allergy prior to study start, and excluded patients with prior diagnoses of OUD. Importantly, in both the unadjusted and adjusted analyses of the unmatched cohort and propensity-score matched sample, the overall study findings and effect size of NSAID allergy on OUD remained similar.

Conclusions

Our findings identify reported NSAID allergies as a risk factor for developing opioid use disorder and receiving opioid prescriptions in adult patients with chronic back pain. This highlights the need for careful clarification of reported drug allergies in general, and NSAID allergies in particular. Establishment and adoption of evidence-based clinical algorithms for management and/or Allergy referral of patients with reported NSAID-induced reactions could be

particularly helpful for non-Allergy providers caring for patients with chronic musculoskeletal pain.

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FIGURE LEGENDS

Figure 1. Association between NSAID adverse reactions and opioid use disorder, in an unadjusted and adjusted analysis of the entire cohort and 1:4 propensity score matched sample. Odds ratios (ORs) and 95% confidence intervals shown.

Table 1. Baseline characteristics of patients with and without reported NSAID adverse drug reactions.

	Exposure group	Comparison group from entire cohort (n=47,114)		Comparison group from 1:4 propensity score matched sample (n=18,100)	
	NSAID ADR, n=3,620	No NSAID ADR, n=43,494	p-value*	No NSAID ADR, n=14,480	Standardized Difference (no ADR vs ADR)
Age, mean [SD]	52 [10]	50 [11]	<0.0001	52 [10]	-0.01
Female sex, count (%)	2,746 (75.9)	27,937 (64.2)	<0.0001	10,984 (75.9)	0
Race/Ethnicity, count (%)					
White	2,545 (70.3)	31,204 (71.7)	0.03	10,180 (70.3)	0
Black	405 (11.2)	4,234 (9.7)		1,620 (11.2)	0
Hispanic	297 (8.2)	3,687 (8.5)		1,188 (8.2)	0
Other / Unknown	373 (10.3)	4,369 (10.0)		1,492 (10.3)	0
Number of inpatient visits in the prior year, count (%)					
0	3,285 (90.7)	40,604 (93.4)	<0.0001	13,299 (91.8)	-0.04
1-2	315 (8.7)	2,722 (6.3)		1,090 (7.5)	0.04
≥3	20 (0.6)	168 (0.4)		91 (0.6)	0.01
Number of outpatient visits in the prior year, count (%)					
0-4	1,167 (32.2)	18,604 (42.8)	<0.0001	4,919 (34.0)	-0.02
5-9	1,069 (29.5)	13,455 (30.9)		4,390 (30.3)	-0.02
≥ 10	1,384 (38.2)	11,435 (26.3)		5,171 (35.7)	0.05
Insurance, count (%)					
Medicaid	805 (22.2)	8,590 (19.7)	<0.0001	3,348 (23.1)	0
Medicare	338 (9.3)	2,839 (6.5)		1,356 (9.4)	-0.02
Dual	488 (13.5)	2,978 (6.8)		1,778 (12.3)	0.04
Private	1,445 (39.9)	22,534 (51.8)		5,761 (39.8)	0
Self-Pay/None	466 (12.9)	5,437 (12.5)		1,926 (13.3)	-0.01
Other	78 (2.2)	1,116 (2.6)		311 (2.1)	0
Medical co-morbidities, count (%)					
Cardiovascular disease	196 (5.4)	1,524 (3.5)	<0.0001	681 (4.7)	0.03
Renal insufficiency	160 (4.4)	880 (2.0)	<0.0001	522 (3.6)	0.04
Connective tissue disease	69 (1.9)	406 (0.9)	<0.0001	268 (1.9)	0
Peptic ulcer disease	82 (2.3)	483 (1.1)	<0.0001	282 (1.9)	0.02
Anxiety	547 (15.1)	4,358 (10.0)	<0.0001	2,141 (14.8)	0.01
Depression	1,451 (40.1)	12,933 (29.7)	<0.0001	5,771 (39.9)	0
Malignancy (except skin)	357 (9.9)	3,962 (9.1)	0.13	1,399 (9.7)	0.01
Chronic idiopathic urticaria**	221 (6.1)	1,075 (2.5)	<0.0001	457 (3.2)	0.14
Allergic rhinitis	714 (19.7)	6,688 (15.4)	<0.0001	2,815 (19.4)	0.01
Asthma	983 (27.2)	6,888 (15.8)	<0.0001	3,883 (26.8)	0.01
Atopic dermatitis	634 (17.5)	6,608 (15.2)	0.0002	2,520 (17.4)	0

*t-tests or Wilcoxon rank sum tests for continuous variables, chi-square for categorical variables

**not included in the propensity score model

ADR, adverse drug reaction; NSAID, non-steroidal anti-inflammatory drug; SD, standard deviation

Table 2. Prevalence of reaction types among patients with chronic back pain and reported NSAID adverse drug reactions (5,187 total listings in 3,620 subjects).

	Number of subjects (%)
Total subjects	3,620
Hypersensitivity	1413 (39.0)
Rash	470 (13.0)
Urticaria or hives	444 (12.3)
Angioedema or swelling	380 (10.5)
Bronchospasm, wheeze	207 (5.7)
Anaphylaxis or hypotension	190 (5.2)
Itching/pruritis	152 (4.2)
Serum sickness	2 (0.1)
Side effect	1,628 (45.0)
Gastrointestinal upset	1,158 (32.0)
Bleed	223 (6.2)
Nausea, vomiting	220 (6.1)
Renal toxicity	71 (2.0)
Dizziness	54 (1.5)
Headache	51 (1.4)
Mental status change	30 (0.8)
Unknown or other reaction	579 (16.0)

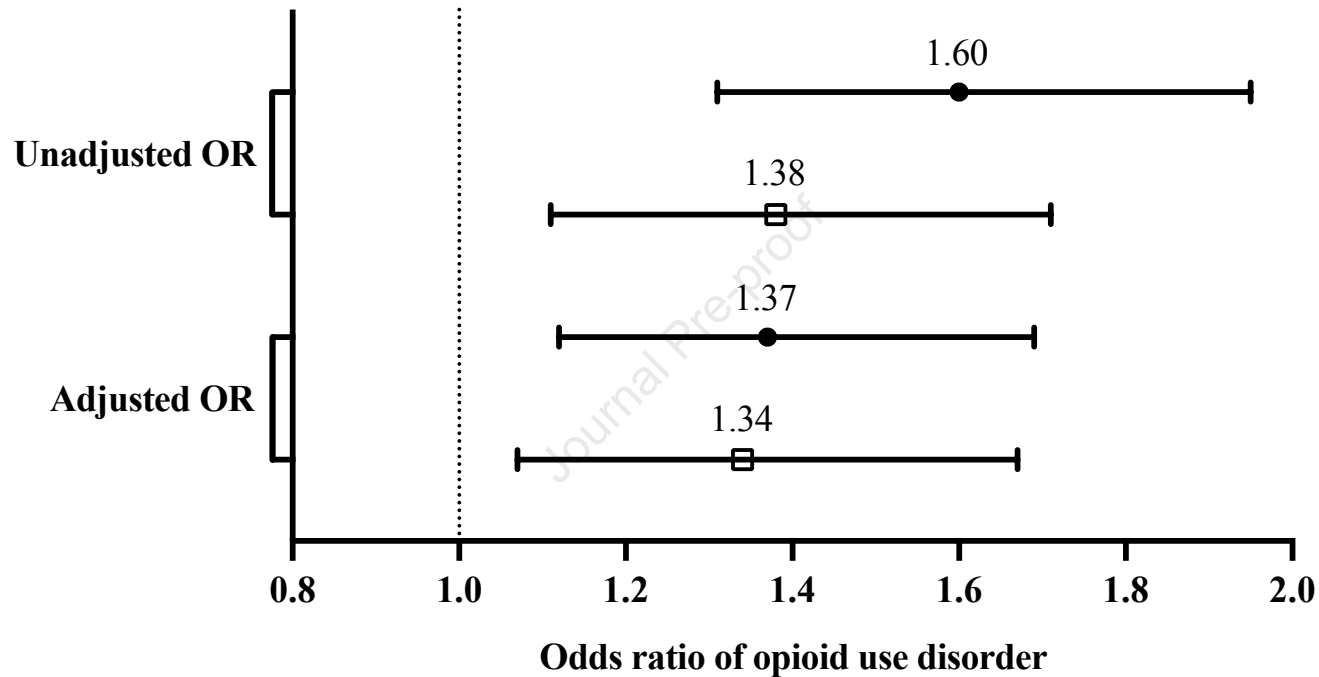
NSAID, non-steroidal anti-inflammatory drug

37 **Table 3.** Predictors of opioid use disorder.

Predictor	Entire cohort		1:4 propensity score matched sample	
	Adjusted Odds Ratio [95% CI]	p-value	Adjusted Odds Ratio [95% CI]	p-value
NSAID adverse drug reaction	1.37 [1.12, 1.69]	0.003	1.34 [1.07, 1.67]	0.01
Age (measured in 10-year increments)	0.70 [0.66, 0.75]	<0.0001	0.70 [0.63, 0.77]	<0.0001
Sex (male vs female)	2.89 [2.52, 3.31]	<0.0001	2.81 [2.28, 3.46]	<0.0001
Race (black vs white)	0.46 [0.36, 0.60]	<0.0001	0.53 [0.38, 0.73]	0.0001
Insurance				
Medicaid vs Private	4.62 [3.84, 5.56]	<0.0001	4.59 [3.36, 6.26]	<0.0001
Medicare vs Private	3.59 [2.77, 4.64]	<0.0001	3.47 [2.33, 5.17]	<0.0001
Dual vs Private	4.99 [4.01, 6.21]	<0.0001	5.25 [3.78, 7.30]	<0.0001
Number of inpatient encounters in the prior year	1.12 [1.01, 1.24]	0.035	1.16 [1.01, 1.33]	0.031
Number of outpatient encounters in the prior year	1.02 [1.02, 1.03]	<0.0001	1.02 [1.01, 1.03]	<0.0001
Comorbidities				
Cardiovascular disease	0.94 [0.70, 1.26]	0.67	0.98 [0.66, 1.45]	0.91
Renal insufficiency	0.70 [0.46, 1.05]	0.09	0.55 [0.31, 0.96]	0.04
Connective tissue disease	1.05 [0.53, 2.10]	0.88	0.90 [0.39, 2.06]	0.80
Peptic ulcer disease	1.47 [0.94, 2.30]	0.10	1.54 [0.90, 2.63]	0.12
Anxiety	1.75 [1.48, 2.07]	<0.0001	1.61 [1.28, 2.03]	<0.0001
Depression	2.34 [2.01, 2.73]	<0.0001	2.22 [1.76, 2.81]	<0.0001
Malignancy (except skin)	0.79 [0.62, 1.01]	0.06	0.71 [0.49, 1.02]	0.06
Allergic rhinitis	0.56 [0.45, 0.70]	<0.0001	0.62 [0.47, 0.82]	0.0009
Asthma	1.37 [1.16, 1.61]	0.0002	1.39 [1.12, 1.72]	0.003
Atopic dermatitis	0.76 [0.63, 0.93]	0.007	0.88 [0.67, 1.15]	0.34

NSAID, non-steroidal anti-inflammatory drug; CI, confidence interval

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● Entire cohort □ 1:4 Propensity score matched sample