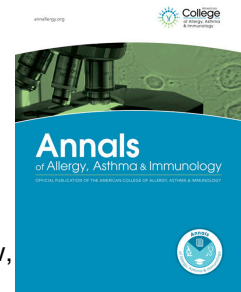


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Reported drug allergies among patients with opioid use disorder: Role for allergy evaluation and intervention

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Title: Reported drug allergies among patients with opioid use disorder: Role for allergy evaluation and intervention

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Key words:

Opioid use disorder; drug allergy; adverse drug reaction; hypersensitivity; non-steroidal anti-inflammatory drug; aspirin; penicillin; beta-lactam; de-labeling

Abbreviations:

ADR – adverse drug reaction

CI – confidence interval

EHR – electronic health record

IRR – incidence rate ratio

NSAID – non-steroidal anti-inflammatory drug

OOD – opioid use disorder

SD – standard deviation

PHS – Partners Healthcare System

Word count: 1042

Tables: 1

Figures: 0

1 Patients with opioid use disorder (OUD) commonly experience infectious complications
2 and challenges surrounding pain management, which contribute to high utilization of the
3 healthcare system.^{1,2}

4 Understanding barriers to providing the most effective care to this patient population is
5 crucial in order to improve patient safety and quality of care and decrease healthcare-related
6 expenditures. In this context, drug allergy over-reporting and inaccurate labeling can lead to
7 unnecessary medication avoidance and increased use of alternative, less effective, or second-line
8 medications with implications for increased morbidity, mortality and economic costs.³⁻⁵ Allergy
9 specialist evaluation in this population may be critical to optimize healthcare treatments and
10 enable more cost-efficient care. However, the prevalence of drug allergies in patients with OUD
11 is unknown. We hypothesized that the prevalence of drug allergies is higher in patients with
12 OUD compared to the general population and explored the associations between reported drug
13 allergies and six-month healthcare utilization patterns in patients with OUD.

14 We analyzed data from 177 consecutive adults (≥ 18 years) with OUD who received care
15 at the Brigham Health Bridge Clinic between 4/2018-8/2019. This specialized clinic was
16 established in April 2018 at Brigham and Women's Hospital in Boston, MA and provides rapid
17 access outpatient care for patients with substance use disorders in all stages of recovery. Subject
18 sociodemographic information, clinical characteristics, and substance use history were obtained
19 from the electronic health record (EHR). Drug allergy status was assessed at the time of the first
20 clinic visit and defined as any adverse drug reaction documented in the EHR. Individual allergy
21 entries underwent manual medical record review to identify frequencies of each implicated drug
22 and associated reaction characteristics. Healthcare utilization was assessed in the six months
23 following the first Bridge Clinic visit.

Negative binomial regression models were built to assess the relationships between reported drug allergies and six-month healthcare utilization outcomes and included a parameter to adjust for person-time given the variable follow-up for individual subjects. Covariates in the multivariable analyses included demographic variables and baseline comorbidities that were associated with each outcome at a significance level of $P < 0.10$, to account for even modest confounders.⁶ In all other analyses, $P < 0.05$ was considered statistically significant. All analyses were performed using RStudio Pro, version 1.2.5033-1. This study was approved by the Mass General Brigham Institutional Review Board.

The majority of subjects in the cohort were male (63.8%) and white (64.4%), and comorbid anxiety, depression, and chronic pain were common (**Table 1**). There were 81/177 (45.8%) patients with at least one documented drug allergy. Patients with reported drug allergies were older (mean 44.5 vs 40.6 years, $P = .02$), and had higher rates of asthma (27.2% vs 13.5%, $P = .04$), hypertension (34.6% vs 17.7%, $P = .01$) and malignancy (9.9% vs 0%, $P = .002$). There was also a trend toward higher rates of depression and chronic pain among patients with, compared to those without, reported drug allergies. Nearly a third of all patients had a history of prior infectious complications related to OUD, with no difference between groups.

Consistent with the published literature, drug allergies were more frequently reported among women (59.4% of all women vs 38.1% of all men, $P = .008$).^{7,8} Women also had a higher number of allergy entries listed per patient compared to men (mean 2.3 [SD 3.7] vs 0.8 [SD 1.4], $P = .001$). Antibiotic allergies were the most commonly reported medication class (26% of all patients), with beta-lactams and sulfonamide antibiotics reported most frequently (15.8% and 7.3% of the entire cohort, respectively). The overall prevalence of nonsteroidal anti-inflammatory drug (NSAID) allergy was 8.5%, with no differences in reporting by sex. There

were also 14.1% of patients with opioid-related entries documented in the EHR, which may be related to the overall higher opioid exposure in this specific patient population. Of 28 total opioid-related entries, a minority involved hives or rash (7) or angioedema (1), with the remainder describing other (15) or unknown (5) reactions.

In an adjusted negative binomial regression model, presence of reported drug allergy was not associated with higher rates of outpatient psychiatry visits (Incidence Rate Ratio [IRR] 0.88, 95% CI 0.70-1.10, $P=.26$) or Emergency Department encounters (IRR 1.55, 95% CI 0.85-2.85, $P=.15$) during the six-month follow-up period. Notably, subjects with reported drug allergies had significantly higher rates of inpatient admissions, compared to patients without reported drug allergies (IRR 1.87, 95% CI 1.07-3.30, $P=.03$). A higher proportion of patients with drug allergies received Emergency Department care for infection (e.g. cellulitis, abscess)- or pain-related reasons (e.g. sciatica, musculoskeletal pain) during the study period (11.1% vs 2.1%, $P=.02$ and 22.2% vs 9.4%, $P=.02$, respectively), and more patients with drug allergies had hospital admissions related to OUD or other substance use disorders (17.3% vs 5.2%, $P=.01$), or infectious etiologies (e.g. osteomyelitis, septic arthritis, bacteremia) (24.7% vs 9.4%, $P=.008$).

Only five patients had ever been evaluated by an Allergist within our health system, and all were seen during an inpatient admission for evaluation of beta-lactam allergy prior to their first outpatient Bridge Clinic visit. Three patients underwent penicillin allergy de-labeling, and two underwent successful cephalosporin desensitization. As a direct result of Allergy evaluation, all patients were able to use the first-line antibiotic specified by the Infectious Disease consult team for treatment of bacteremia, osteomyelitis, and/or abscess. This highlights the clear benefits of Allergy evaluation of reported drug allergies in this population.

In conclusion, antibiotic and NSAID allergies are more commonly reported among patients with OUD than previously published rates for the general population.⁷⁻⁹ Roughly a third of patients had a history of infectious complications and comorbid chronic pain, highlighting the important role of antibiotics and NSAIDs in the care of this patient population. Reported drug allergies were also associated with higher six-month inpatient hospital utilization patterns. Due to our small cohort size, we did not study other OUD-related outcomes such as treatment retention, overdose rates, or toxicology patterns which could represent other contributing factors to the differences in healthcare utilization observed in this study. Future prospective work is warranted to further elucidate the impact of drug allergy labels on and temporal relationships with clinical outcomes in diverse patient groups. Patients with OUD, and particularly those with a history of infectious complications, chronic pain, or anticipated surgery and a history of beta-lactam and/or NSAID allergies, may benefit greatly from early allergy referral with dedicated drug allergy evaluation, intervention, and possible de-labeling by drug challenge.

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Table 1. Cohort demographics

	Total cohort, n=177	No reported medication allergy, n=96	Reported medication allergy, n=81	<i>P</i> value*
Age in years, mean [SD]	42.4 [11.4]	40.6 [11.0]	44.5 [11.4]	.02
Male, count (%)	113 (63.8%)	70 (72.9%)	43 (53.1%)	.008
Race/ethnicity, count (%)				.05
White	114 (64.4)	54 (56.2)	60 (74.1)	
Black	24 (13.6)	13 (13.5)	11 (13.6)	
Hispanic	25 (14.1)	20 (20.8)	5 (6.2)	
Other	7 (4.0)	4 (4.2)	3 (3.7)	
Not available	7 (4.0)	5 (5.2)	2 (2.5)	
Co-morbidities, count (%)				
Anxiety	107 (60.5)	54 (56.3)	53 (65.4)	.22
Depression	120 (67.8)	59 (61.5)	61 (75.3)	.054
Chronic pain	61 (34.5)	27 (28.1)	34 (42.0)	.059
Hepatitis C	77 (43.5)	37 (38.5)	40 (49.4)	.17
Hypertension	45 (25.4)	17 (17.7)	28 (34.6)	.01
Renal disease	8 (4.5)	4 (4.2)	4 (4.9)	1.0
Diabetes	19 (10.7)	8 (8.3)	11 (13.6)	.33
Malignancy	8 (4.5)	0 (0)	8 (9.9)	.002
Asthma	35 (19.8)	13 (13.5)	22 (27.2)	.04
Allergic rhinitis	10 (5.6)	3 (3.1)	7 (8.6)	.19
Atopic dermatitis	5 (2.8)	3 (3.1)	2 (2.5)	1.0
History of prior infectious complication, count (%)	56 (31.6)	31 (32.3)	25 (30.9)	.87
History of prior allergy evaluation, count (%)	5 (2.8)	2 (2.1)	3 (3.7)	.66

**t*-test or Wilcoxon rank sum test for continuous variables, Fisher's exact or chi-square test for categorical variables

Abbreviations: SD, standard deviation

Boldface indicates $P < .05$