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Kevin W. McConeghy

R. Caffrey

University of Rhode Island, [aisling\\_caffrey@uri.edu](mailto:aisling_caffrey@uri.edu)

Haley J. Morrill

University of Rhode Island

Amal N. Trivedi

Kerry L. LaPlante

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University of Rhode Island, [kerrylaplante@uri.edu](mailto:kerrylaplante@uri.edu)

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Are non-allergic drug reactions commonly documented as medication "allergies"? A national cohort of Veterans' admissions from 2000-2014.

Kevin W. McConeghy, Pharm.D., M.S.<sup>1, 2</sup>

Aisling Caffrey, Ph.D.<sup>1, 2, 3, 4</sup>

Haley J. Morrill, Pharm.D.<sup>1, 2, 4</sup>

Amal N. Trivedi, M.D., M.P.H.<sup>1, 3</sup>

Kerry L. LaPlante, Pharm.D.<sup>1, 2, 4, 5</sup>

Affiliations:

<sup>1</sup>Center of Innovation in Long Term Services and Supports, Veterans Affairs Medical Center, Providence VA Medical Center, Providence, RI

<sup>2</sup>Infectious Diseases Research Program, Veterans Affairs Medical Center, Providence, RI

<sup>3</sup>Department of Health Services, Policy and Practice, School of Public Health, Brown University, Providence, RI

<sup>4</sup>Department of Pharmacy Practice, College of Pharmacy, University of Rhode Island, North Kingston, RI

<sup>5</sup>Warren-Albert School of Medicine, Brown University, Providence, RI

Author contributions:

Study design: KWM, KL, AC

Data Analysis: KWM

Manuscript editing: KWM, KL, AC, HJM, ANT

## **Abstract**

**Purpose.** Adverse drug reactions (ADR) including medication allergies are not well-described among large national cohorts. This study described the most common documented medication allergies and their reactions among a national cohort of Veterans Affairs (VA) inpatients.

**Methods.** We evaluated inpatient admissions in any VA Medical Center from 1/1/2000 to 12/31/2014. Each admission was linked with allergy history preceding or upon admission. Individual drugs were aggregated into drug class category including: penicillins, sulfonamides, angiotensin converting enzyme (ACE) inhibitors, opiates, HMG-CoA reductase inhibitors (“statins”) and non-steroidal anti-inflammatory inhibitors (NSAID). Results were reported in aggregate and over time.

**Results.** Approximately ~10.8 million inpatient admissions occurred from 2000 – 2014. We found the most commonly reported allergy drug classes were penicillins (13%, n=1,410,080), opiates (9.1%, n=984,978), ACE inhibitors (5.7%, n=618,075) sulfonamides (5.1%, n=558,653), NSAIDs (5.1%, n=551,216) and statins (3.6%, n=391,983). Several allergy histories increased over time including opiates (6.2 to 11.2%), ACE inhibitors (1.3 to 10.2%), statins (0.3 to 7.3%) and NSAIDs (3.9 to 6.0%). Rash was the most commonly documented reaction on reports for penicillins (25.5%, n=371,825), sulfonamides (25.6%, n=165,954), and NSAIDs (10.3%, n=65,741). The most common reaction for opiates was nausea/vomiting (17.9%, n=211,864), cough/coughing for ACE inhibitors (41.0%, n=270,537) and muscle pain/myalgia for statins (34.1%, n=186,565).

**Conclusions.** We report that penicillins and opiates are the most commonly documented drug allergies among VA inpatients, but other drug classes such as ACE inhibitors, statins and NSAIDs are becoming increasingly common. Clinicians also commonly document non-allergic ADRs in the allergy section such as cough or myalgia.

## **Introduction**

Adverse drug reactions (ADR) including medication allergies are a common and burdensome reality in patients' treatment. However ADRs are difficult to study in large databases because they are often not identified in health claims or other reports.<sup>1, 2</sup> Allergy databases may represent an important potential data source for studying ADRs. Thus, we undertook a study to describe the most common documented medication allergies and their reactions among inpatients receiving care in the Veterans Affairs (VA) health care system. We focused on the VA health care system for two reasons. First, the VA is the nation's largest integrated health care delivery system, caring for approximately 9 million Veterans and operating 144 medical centers and 1200 outpatient clinics throughout the US.<sup>3</sup> Second, the VA's comprehensive electronic health record includes detailed information on documented "allergies" to specific medications.

## **Methods**

We evaluated inpatient admissions in any VA Medical Center from 1/1/2000 to 12/31/2014. Admissions included acute care as well as short-stay observations, domiciliary stays, or long-term nursing care stays during the study period. Each unique admission was linked with allergy history preceding or upon admission. Allergy histories correspond to the general allergy section of the electronic medical record and could be documented from a variety of previous health encounters (e.g. previous admission, outpatient clinic or pharmacy visit). Individuals without any allergy records were assumed to have no known drug allergies. For comparison to previous studies, we identified individual drugs and combined them into their respective drug class

category.<sup>4,5</sup> Natural and other synthesized penicillins were combined into one “penicillin-class” category (e.g. penicillin, ampicillin, amoxicillin, methicillin, dicloxacillin, oxacillin, nafcillin, piperacillin, carbenicillin and ticarcillin). Sulfonamides included documented “sulfa” allergies not otherwise specified or specific sulfonamide antibiotic (trimethoprim, sulfacetamide, sulfadiazine, sulfamethoxazole, sulfasalazine and dapsone). Angiotensin converting enzyme (ACE) inhibitors included lisinopril, enalapril, ramipril, quinapril, perindopril, benazepril, fosinopril and captopril. Opiates included codeine, morphine, fentanyl, hydromorphone, oxycodone, methadone and meperidine. HMG-CoA reductase inhibitors (“statins”) included simvastatin, atorvastatin, rosuvastatin, pravastatin, fluvastatin and lovastatin. Non-steroidal anti-inflammatory inhibitors (NSAID) included aspirin, ibuprofen, naproxen, indomethacin, ketorolac, diclofenac, sulindac, etodolac, piroxicam and meloxicam. This study was approved by the Providence VA Institutional Review Board and Research and Development Committee.

## **Results**

Overall we identified 2,948,543 patients with 10,858,398 admissions from 2000 – 2014. These admissions were included from 127 VA Medical Centers across 48 states, Washington D.C. and Puerto Rico. Among admissions, 95.2% (n=10,339,233) were male, with a mean age of 63 ( $\pm$  14 years). We found the most common allergies were penicillins (13%, n=1,410,080), opiates (9.1%, n=984,978), ACE inhibitors (5.7%, n=618,075) sulfonamides (5.1%, n=558,653), NSAIDs (5.1%, n=551,216) and statins (3.6%, n=391,983). The most common individual drugs included penicillin, codeine, lisinopril, simvastatin, morphine, aspirin and trimethoprim/sulfamethoxazole (Table 1). Penicillins and sulfonamides allergies increased  $\leq$ 1% during the study period (Figure 1).

The other allergy histories that increased over time included opiates (6.2 to 11.2%), ACE inhibitors (1.3 to 10.2%), statins (0.3 to 7.3%) and NSAIDs (3.9 to 6.0%).

Missing documentation about reactions was common ranging from 22.5 to 43.3% of reports by drug class (Table 1). Rash was the most commonly documented reaction on reports for penicillins (25.5%, n=371,825), sulfonamides (25.6%, n=165,954), and NSAIDs (10.3%, n=65,741). The most common reaction for opiates was nausea/vomiting (17.9%, n=211,864). Cough/coughing was the most common reaction for ACE inhibitor allergy reports (41.0%, n=270,537). Statin allergies most commonly stated a muscle pain/myalgia reaction on reports (34.1%, n=186,565).

## **Discussion**

We report that penicillins and opiates are the most commonly documented drug allergies among inpatients in the VA system, but other drug classes such as ACE inhibitors, statins and NSAIDs are becoming increasingly common. Previous studies have found similar rates of penicillin allergies, and it is commonly reported that 10-15% of admitted patients are allergic to penicillins.<sup>6-9</sup> A similarly designed study of health care plan members in the Southern California Kaiser Permanente system, which included both inpatients and outpatients found overall lower allergy prevalence rates (penicillin [7.9%], sulfonamide [4.3%], narcotic [3.7%], NSAIDs [2.1%], ACE inhibitors [1.3%]) than our study.<sup>5</sup> However, they also found ACE inhibitors, NSAIDs and narcotics to be among the most commonly reported allergies. Only one other published study has investigated documented allergy trends over time.<sup>4</sup> This single-center study which evaluated allergy prevalence from 1990-2013 reported similar prevalence findings for penicillins (12.8%), ACE inhibitors (2.0%), sulfonamides (7.4%), opiates (6.8%), and

NSAIDs (3.5%), as well as demonstrating a similar increase in ACE inhibitor, opiate, and statin allergies over time. Few studies have described the type of reactions reported by patients/providers. In a single-center study with retrospective chart review and patient interview which evaluated documented antimicrobial allergies and patient reported reactions, type I-IV hypersensitivity for penicillins and sulfonamides were classified for 69/198 [35%] and 28/88 [32%] of allergies respectively.<sup>12</sup> A large national evaluation of outpatient medical records demonstrated that the presence of an “allergic-like event” (a combined definition of anaphylaxis, urticaria, angioedema and severe skin reactions) to penicillin does increase the likely occurrence of another reaction to cephalosporin or sulfonamide, but serious allergic hypersensitivities are relatively rare overall (<0.001%).<sup>13</sup>

In our study, the large number of ACE inhibitor and statin “allergies” and their increase over time was unanticipated. ACE inhibitor and statin allergic hypersensitivities have not previously been described with comparable frequency to opiates and sulfonamide drugs.<sup>10</sup> Documentation is subject to the historian judgment and patient recall, therefore the term “allergy” could also refer to other serious non-allergic ADRs which were deemed appropriate to document at the time. This is supported by our findings on the most commonly described reactions with each drug (Table 1).

Clinicians may document non-allergic ADRs in the allergy domain to inform other providers to avoid these medications, such as ACE inhibitor-induced cough or muscle pain from statin therapy. These commonly reported ADRs (e.g. ACE inhibitor cough) raise the possibility that the “allergy” histories of VA patients (and possibly other electronic medical record systems) may contain substantial information on a variety of

historical adverse drug reactions not just allergic reactions. Review of allergy domains in electronic medical record systems may prove to be an untapped source for pharmacovigilance and post-marketing surveillance of medications. Future electronic health record (EHR) innovations could explicitly divide these sections into “allergy”, “intolerance”, and “food” to reduce this technical inaccuracy. A system which allows for greater specificity in documenting drug and food reactions could improve patient safety as clinicians will be able to make better informed decisions for patient management in the presence of such reaction histories. A significant limitation to this approach may be the accuracy of the documented allergy. Inaccuracy in documentation can be two-fold, 1) the history could be inaccurately recorded or 2) the history even when accurately taken from the patient may not actually be related to any real hypersensitivity. Patients with documented penicillin allergies often do not have physiologic reactions, but among other documented “allergies” the overall likelihood of actual ADRs after rechallenge is not well-described.<sup>14</sup> One study compared documented allergy records vs. actual patient interview in an emergency department setting and found significant discordance.<sup>15</sup>

In our study, the reactions reported generally reflect the ADR profile of that agent (i.e. cough, angioedema, hyperkalemia for ACE inhibitors; Table 1) and even if the allergy documentation is inaccurate, these “allergies” could still be useful as they influence treatment decisions regardless of the accuracy.<sup>8</sup> Therefore, we highlight the opportunity to investigate documented “allergies” with regards to general ADR trends and how they impact drug utilization and health outcomes.

**Ethics Statement**

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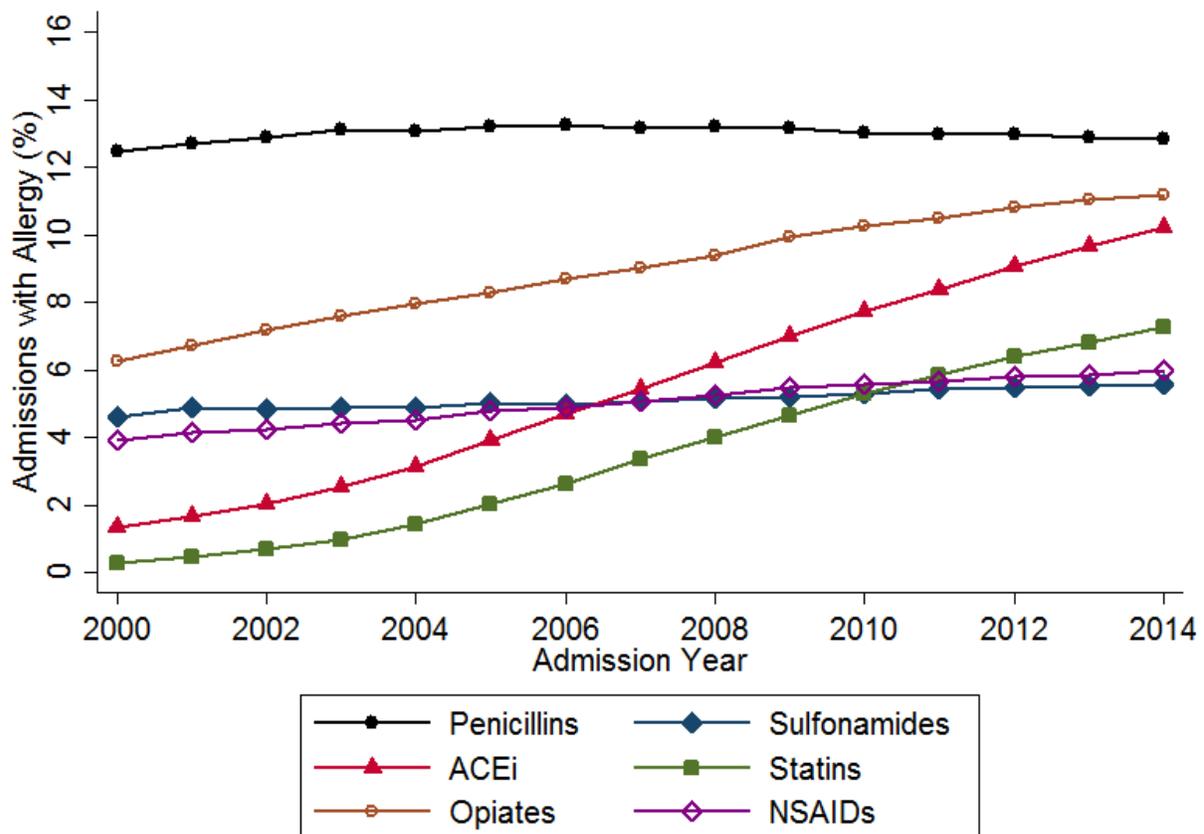
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**Document Allergies Over Time, 2000-2014**

	Penicillins	Opiates	ACE inhibitors	Sulfonamides	NSAID	Statins
Admissions with any allergy	1,410,080 (13.0)	984,978 (9.1)	618,075 (5.7)	558,653 (5.1)	551,216 (5.1)	391,983 (3.6)
By drug <sup>a</sup> (% of class)	Penicillin	Codeine	Lisinopril	NOS	Aspirin	Simvastatin
	1,289,229 (91.4)	526,825 (53.5)	474,567 (76.8)	414,214 (74.1)	251,907 (45.7)	307,316 (78.4)
	Amoxicillin	Morphine	NOS	TMP/SMX	Ibuprofen	Atorvastatin
	96,348 (6.8)	268,332 (27.2)	62,380 (10.1)	188,792 (33.8)	171,730 (31.2)	64,025 (16.3)
	Ampicillin	Oxycodone	Fosinopril	Sulfacetamide	Naproxen	Pravastatin
	37,211 (2.6)	121,870 (12.4)	61,778 (10.0)	17,165 (3.1)	69,599 (12.6)	48,659 (12.4)
	Piperacillin	Meperidine	Enalapril	Sulfasalazine	Ketorolac	Rosuvastatin
17,939 (1.3)	95,179 (9.7)	19,694 (3.2)	7,924 (1.4)	34,169 (6.2)	37,865 (9.7)	
Dicloxacillin	Hydrocodone	Benazepril	Sulfadiazine	Indomethacin	Fluvastatin	
7,275 (0.5)	92,661 (9.4)	16,575 (2.7)	4,956 (0.9)	26,815 (4.9)	29,045 (7.4)	
Total allergies <sup>b</sup>	1,458,269	1,181,299	660,563	647,948	638,643	547,168
By reaction <sup>c</sup> (% of allergies)	Rash	Nausea/vomiting	Cough/coughing	Rash	Rash	Muscle pain/myalgia
	371,825 (25.5)	211,864 (17.9)	270,537 (41.0)	165,954 (25.6)	65,741 (10.3)	186,565 (34.1)
	Hives/urticaria	Rash	"Other"	Hives/urticaria	Nausea/vomiting	"Other"
	201,828 (13.8)	130,176 (11.0)	43,946 (6.7)	67,806 (10.5)	64,208 (10.1)	50,609 (9.2)
	"Other"	Hives/urticaria	Angioedema	"Other"	"Other"	Weakness
	62,036 (4.3)	75,202 (6.4)	42,312 (6.4)	33,515 (5.2)	60,919 (9.5)	22,316 (4.1)
	Swelling/ edema	"Other",	Hyperkalemia	Nausea/vomiting	Hives/urticaria	Rash
85,687 (5.9)	58,143 (4.9)	28,968 (4.4)	32,652 (5.0)	41,897 (6.6)	18,742 (3.4)	
Anaphylaxis	Pruritis	Rash	Anaphylaxis	GI reaction	Diarrhea	
45,573 (3.1)	12,695 (1.1)	21,445 (3.2)	8,310 (1.3)	15,471 (2.4)	11,666 (2.1)	
Missing reaction	632,073 (43.3)	415,459 (35.2)	148,629 (22.5)	273,798 (42.3)	247,827 (38.8)	133,793 (24.5)

**Description.** Total admissions (n=10,858,398). The most common allergy classes, individual drugs and the most common reactions reported. ACE – angiotensin converting enzyme, NSAID – non-steroidal anti-inflammatory drugs, N/V – Nausea/Vomiting, GI - gastrointestinal. NOS – Not otherwise specified. TMP/SMX – Trimethoprim/Sulfamethoxazole.

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- a- An individual admission could have multiple allergies in the same class listed so these values exceed the “any allergy” count (e.g. patient had both penicillin and amoxicillin listed).
  - b- “Total allergies” refers to unique individual allergy records per admission (vs. any allergy).
  - c- Each allergy could have more than one recorded reaction so reaction counts exceed total allergies. Allergy histories stated “other reaction” for many entries.



**Figure 1.** Veteran Health Administration documented “allergies” among inpatient admissions from 2000 - 2014. ACEi – angiotensin converting enzyme inhibitors, NSAIDs – non-steroidal anti-inflammatory drugs.