

BRIEF REPORT

Are non-allergic drug reactions commonly documented as medication “allergies”? A national cohort of Veterans’ admissions from 2000 to 2014

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ABSTRACT

Purpose Adverse drug reactions (ADRs) 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 January 2000 to 31 December 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 to 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. Copyright © 2016 John Wiley & Sons, Ltd.

KEY WORDS—allergy; drug safety; Veterans; inpatient; adverse drug reaction; pharmacoepidemiology

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INTRODUCTION

Adverse drug reactions (ADRs) 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.^{1,2} 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

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144 medical centers and 1200 outpatient clinics throughout the US.³ 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 January 2000 to 31 December 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.^{4,5} 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 to 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 (± 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.^{6–9} 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.⁵ However, they also found ACE inhibitors, NSAIDs and narcotics to be among the most commonly reported allergies. At least one other published study has investigated documented allergy trends over time.⁴ This single-center study which evaluated allergy prevalence from 1990 to 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

Table 1. Most commonly documented allergies and reactions among VA admissions from 2000 to 2014, no. (%)

	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 ^a	Penicillin 1 289 229 (91.4)	Codeine 526 825 (53.5)	Lisinopril 474 567 (76.8)	NOS 414 214 (74.1)	Aspirin 251 907 (45.7)	Simvastatin 307 316 (78.4)
(% of class)	Amoxicillin 96 348 (6.8)	Morphine 268 332 (27.2)	NOS 62 380 (10.1)	TMP/SMX 188 792 (33.8)	Ibuprofen 171 730 (31.2)	Atorvastatin 64 025 (16.3)
	Ampicillin 37 211 (2.6)	Oxycodone 121 870 (12.4)	Fosinopril 61 778 (10.0)	Sulfacetamide 17 165 (3.1)	Naproxen 69 599 (12.6)	Pravastatin 48 659 (12.4)
	Piperacillin 17 939 (1.3)	Meperidine 95 179 (9.7)	Enalapril 19 694 (3.2)	Sulfasalazine 7924 (1.4)	Ketorolac 34 169 (6.2)	Rosuvastatin 37 865 (9.7)
	Dicloxacillin 7275 (0.5)	Hydrocodone 92 661 (9.4)	Benazepril 16 575 (2.7)	Sulfadiazine 4956 (0.9)	Indomethacin 26 815 (4.9)	Fluvastatin 29 045 (7.4)
Total allergies ^b	1 458 269	1 181 299	660 563	647 948	638 643	547 168
By reaction ^c	Rash 371 825 (25.5)	Nausea/vomiting 211 864 (17.9)	Cough/coughing 270 537 (41.0)	Rash 165 954 (25.6)	Rash 65 741 (10.3)	Muscle pain/myalgia 186 565 (34.1)
(% of allergies)	Hives/urticaria 201 828 (13.8)	Rash 130 176 (11.0)	"Other" 43 946 (6.7)	Hives/urticaria 67 806 (10.5)	Nausea/vomiting 64 208 (10.1)	"Other" 50 609 (9.2)
	"Other" 62 036 (4.3)	Hives/urticaria 75 202 (6.4)	Angioedema 42 312 (6.4)	"Other" 33 515 (5.2)	"Other" 60 919 (9.5)	Weakness 22 316 (4.1)
	Swelling/edema 85 687 (5.9)	"Other", 58 143 (4.9)	Hyperkalemia 28 968 (4.4)	Nausea/vomiting 32 652 (5.0)	Hives/urticaria 41 897 (6.6)	Rash 18 742 (3.4)
Missing reaction	Anaphylaxis 45 573 (3.1)	Pruritis 12 695 (1.1)	Rash 21 445 (3.2)	Anaphylaxis 8310 (1.3)	GI reaction 15 471 (2.4)	Diarrhea 11 666 (2.1)
	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.

^aAn 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).

^bTotal allergies" refers to unique individual allergy records per admission (vs. any allergy).

^cEach allergy could have more than one recorded reaction so reaction counts exceed total allergies. Allergy histories stated "other reaction" for many entries.

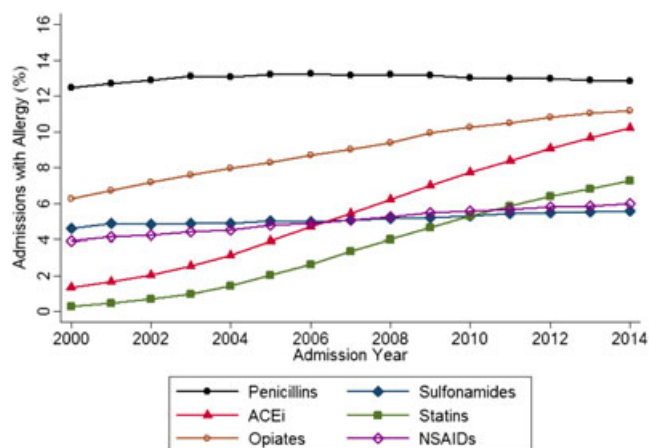


Figure 1. Veteran Health Administration documented “allergies” among inpatient admissions from 2000 to 2014. ACEi—angiotensin converting enzyme inhibitors, NSAIDs—non-steroidal anti-inflammatory drugs

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.¹⁰ 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%).¹¹

In our study, the large number of ACE inhibitor and statin “allergies” and their increase over time were unanticipated. ACE inhibitor and statin allergic hypersensitivities have not previously been described with comparable frequency to opiates and sulfonamide drugs.¹² 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 ADRs 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: (i) the history could be inaccurately recorded or (ii) 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.¹³ One study compared documented allergy records versus actual patient interview in an emergency department setting and found significant discordance.¹⁴

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.⁸ 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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AUTHOR CONTRIBUTIONS

Study design: KWM, KL, AC

Data Analysis: KWM

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

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