



Spontaneous cutaneous adverse drug reaction reports—An analysis of a 10-year dataset in Singapore

Si Xian Wong¹ | Mun Yee Tham² | Chee Leok Goh³ | Han Hui Cheong⁴  |
Sui Yung Chan¹ 

¹Department of Pharmacy, Faculty of Science, National University of Singapore, Singapore, Singapore

²Vigilance and Compliance Branch, Health Sciences Authority, Singapore, Singapore

³National Skin Centre, Singapore, Singapore

⁴Department of Pharmacy, KK Women's and Children's Hospital, Singapore, Singapore

Correspondence

Sui Yung Chan, Department of Pharmacy, National University of Singapore, Singapore.
Email: suiyungchan@nus.edu.sg

Abstract

We analyzed the spontaneous adverse event database in Singapore to determine the types of cutaneous adverse drug reactions (CADRs) and causative drugs reported. We selected 10 CADRs-of-interest, and identified the suspected drugs and the characteristics of the at-risk population. ADR reports received from 2006 to 2015 of the system organ class “Skin and Appendages Disorders” were analyzed based on patient demographics, the types of CADRs, suspected drugs, outcome, and latency period. Of the 104 372 reports analyzed, 56.2% involved females and 72.5% involved Chinese patients. The mean age was 41.1 years old. The top CADRs reported were rash (including nonspecified rash, follicular rash, maculopapular rash, and vesicular rash) (67.2%) and angioedema (13.9%). The drugs frequently associated with the CADRs-of-interest include nonsteroidal antiinflammatory drugs and antibiotics with angioedema, iohexol with urticaria, and antiepileptics and allopurinol with Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN). A subgroup analysis based on age, sex, and race on the 10 CADRs-of-interest showed the following trends in reporting: Alopecia (reported more in females), drug hypersensitivity syndrome (more in males), angioedema (more in younger patients), and photosensitivity (more in older patients). In general, the racial distribution across each CADR-of-interest was consistent with that of Singapore's population, with slight deviations observed for SJS/TEN, photosensitivity and skin discoloration. We analyzed CADR reports from Singapore over 10 years, and identified the types of CADRs reported, and their associated drugs, latency periods and patient characteristics. Such information could add value to healthcare professionals as they assess CADR cases and evaluate suspected drugs.

KEYWORDS

adverse drug reactions pharmacovigilance, skin, spontaneous reporting

Abbreviations: ADR, adverse drug reaction; CADRs, cutaneous ADRs; CADR, cutaneous adverse drug reactions; SJS, Stevens-Johnson syndrome; SOC, system organ class; TEN, toxic epidermal necrolysis; WHO, World Health Organisation.

Si Xian Wong and Mun Yee Tham should be considered joint first author.

This study has neither been previously published nor presented at any conferences.

This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

© 2019 The Authors. *Pharmacology Research & Perspectives* published by John Wiley & Sons Ltd, British Pharmacological Society and American Society for Pharmacology and Experimental Therapeutics.

1 | INTRODUCTION

According to the World Health Organisation (WHO), an adverse drug reaction (ADR) is a response to a medicinal product which is noxious and unintended and which occurs at doses normally used in man.¹ Cutaneous ADRs (CADRs) are one of the most common ADRs,²⁻⁴ with an overall incidence rate of 2%-3% in hospitalized patients.⁵ In the WHO global ADR database, Vigibase, skin and appendages disorders account for 18.3% of over 13 million ADR reports received from more than 100 countries, making it the third most frequently reported system organ class (SOC).^{6,7} As the national regulatory agency in Singapore, the Health Sciences Authority (HSA) receives around 20 000 ADR reports annually in the adverse event (AE) database, of which 60% were related to skin reactions.

The manifestation of CADRs can be very varied, ranging from mild, self-limiting reactions to severe cutaneous adverse reactions (SCARs) associated with significant morbidity and mortality, such as acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug hypersensitivity syndrome (DHS). CADRs are also associated with a wide range of drugs, with antimicrobials, NonSteroidal Anti-Inflammatory Drugs (NSAIDs), antiepileptics, and analgesics as the most frequently implicated drug classes.⁸⁻¹² While much is known about CADRs, information on the types of CADRs reported through the spontaneous ADR reporting system is limited. We seek to fill this knowledge gap with an analysis of a large dataset with over 100 000 CADR reports from a 10-year period from the HSA AE database. Our objectives are to determine the types of CADRs and associated drugs reported to the HSA AE database, to identify characteristics of the at-risk population, and to identify associations between CADRs and drugs.

2 | MATERIALS AND METHODS

2.1 | Data source

In Singapore, spontaneous AE reports are submitted to HSA and captured into the national AE database. These reports come primarily from healthcare professionals via the Critical Medical Information Store (CMIS) or by email, online, fax, or post. The CMIS, a data repository for ADRs, drug allergies and medical alerts, allows healthcare professionals to enter AE information into the patient's electronic medical record, and this information is then transmitted to HSA, making reporting of AEs a seamless process. Since the introduction of CMIS in 2006, the number of reports received by HSA has increased exponentially, from 1185 reports in 2005 to 10 685 in 2006 and stabilizing at about 20 000 reports annually since 2010, facilitating the detection of potential drug safety signals.

For each report, AEs were coded using the WHO Adverse Reaction Terminology (WHO-ART), drugs were classified using the Anatomical Therapeutic Chemical (ATC) Classification System, and

causality was assessed based on the WHO Uppsala Monitoring Centre (WHO-UMC) causality assessment system.

2.2 | Inclusion criteria

Spontaneous AE reports which met the following criteria were included in our study: (1) report was received between 2006 and 2015, (2) reported AE belongs to the SOC of "Skin and Appendages Disorders" and (3) causality was assessed as certain, probable or possible.

2.3 | Data extraction, collation, and analysis

Anonymized data with basic demographic information, reporters' profession, AE description, patient outcome, and suspected drug(s) were extracted from the AE database.

To facilitate analysis, WHO-ART preferred terms used for coding the CADRs were grouped into 21 reaction types. From these, 10 CADRs-of-interest were selected for in-depth analysis based on clinical relevance.

2.4 | Statistical analysis

All variables were analyzed by applying descriptive statistics using Statistical Package for the Social Sciences (SPSS) Inc., Chicago, IL, USA, version 24.0.

This study was approved by the National University of Singapore Institutional Review Board.

3 | RESULTS

Out of 178 810 AE reports captured between 2006 and 2015, 104 372 AE reports belonging to the SOC of "Skin and Appendages Disorder" were included in our analysis, and their characteristics are provided in Table 1. The mean patient age was 41.1 years old, with a bimodal distribution peaking at 20-29 years old (16.9%) and 50-59 years old (15.7%). A majority of the CADR reports involved Chinese (72.5%), in tandem with the country's demographics, and female patients (56.2%). Most of the CADRs were reported by doctors (91.9%), and were associated with Western health products (98.6%). About slightly more than half of the CADRs reported were assessed as nonserious (59.2%).

The types of CADRs reported and their frequencies are listed in Table 2. Rash (including nonspecified rash, follicular rash, maculopapular rash, and vesicular rash) was most frequently reported (67.2%), followed by angioedema (13.9%) and pruritus (7.4%). SCARs such as SJS/TEN, AGEP and pustular rash, and DHS were reported less frequently, in 0.7%, 0.5%, and 0.2% of the reports, respectively.

Table 3 shows the top 10 drug classes, and the respective top five drugs in each class. Systemic antibacterials were most commonly implicated (43.5%) followed by antiinflammatory and antirheumatic

TABLE 1 Demographic characteristics of patients and characteristics of reports with AEs belonging to SOC “Skin and Appendages Disorder”

Demographics of patients	%	Characteristics of report	%
Sex ^a		Types of Product	
Male	43.8	Western	98.6
Female	56.2	Vaccines	0.5
Age (Mean = 41.1 years old; Range = 0 to 115 years old) ^a		Health supplements	0.4
0-9	6.6	Biologics (excluding vaccines)	0.3
10-19	10.5	Complementary medicine	0.1
20-29	16.9	Cosmetics	<0.1
30-39	14.2	Medical device	<0.1
40-49	14.4	Others	<0.1
50-59	15.7	Information unavailable	<0.1
60-69	11.4	Assessment of causality	
70-79	6.7	Possible	97.1
≥ 80	3.5	Probable	2.4
		Certain	0.5
Race ^a		Assessment of seriousness ^b	
Chinese	72.5	Serious	40.8
Malay	12.5	Not Serious	59.2
Indian	8.1	Reporter's profession	
Others	7.0	Doctor	91.9
		Pharmacist	6.4
		Dentist	0.7
		Nurse	0.4
		Drug company	0.4
		Research coordinator	< 0.1
		Others	< 0.1
		Consumer	< 0.1

^aOut of 104 372 CADR reports, sex, age, and race were not reported in 2.8%, 5.9%, and 12.1% of the reports, respectively, and these were excluded from the figures.

^bSeriousness is assessed based on the International Conference of Harmonisation (ICH) E2A guidelines.

products (16.2%) and analgesics (9.0%). Antiepileptics made up 1.6% of the suspected drugs, and was ranked seventh.

Only 10.8% of reports specified the patient's outcome, with 2040 (2.0%) and 9159 reports (8.8%) indicating that the patient has yet to recover at the time of reporting, or have recovered, respectively. Out of the 92 (0.1%) reports with fatal outcome, nine were assessed as unrelated to the drug, while 83 could be related to the drug or adverse reaction. For fatal reports assessed as related, SJS/TEN ($n = 53$, 63.9%) had the highest number of reports. Allopurinol ($n = 23$, 27.7%) was the top suspected drug.

Table 4 lists the 10 CADRs-of-interest and their top 10 suspected drugs. Antibacterials and NSAIDs were frequently associated with all types of CADRs, with the exception of alopecia.^{13,14} Antiepileptics and allopurinol were commonly implicated in SJS/TEN and DHS.

For each CADR-of-interest, a subgroup analysis was performed based on age, sex, race, and latency of reaction (Table 5). Alopecia had the lowest male/female ratio at 0.28 while DHS had the highest

at 1.40. Angioedema was reported by younger patients (median age = 34 years) while photosensitivity, DHS and SJS/TEN were reported by older patients (median age = 50-58 years). In general, the racial distribution across each CADR-of-interest was consistent with that of Singapore's population, with trending towards the Malays, Chinese and Indians for SJS/TEN, photosensitivity and skin discoloration, respectively. These trends remained even after taking into account the population size¹⁵ of each race to estimate the frequency of each CADR-of-interest across races. The latency period for CADRs also varies, from acute ones (eg angioedema, urticaria) to those which take weeks to occur (eg photosensitivity, alopecia).

4 | DISCUSSION

In this study, we analyzed a large volume of spontaneous AE reports and highlighted the various patterns of CADRs and their implicated

No.	Reaction type	Frequency (N)	%
-	Total	108 798 ^a	100.00
1	Rash (includes nonspecified rash, follicular rash, maculopapular rash, vesicular rash)	73 074	67.2
2	Angioedema	15 177	13.9
3	Pruritus	8065	7.4
4	Urticaria	7704	7.1
5	Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis (SJS/TEN)	813	0.7
6	Fixed Drug Eruption (FDE)	790	0.7
7	Acute Generalized Exanthematous Pustulosis (AGEP) and pustular rash	510	0.5
8	Bullous eruption	488	0.4
9	Erythema multiforme	311	0.3
10	Generalized exfoliative dermatitis	296	0.3
11	Dermatitis (includes eczema, contact dermatitis, nonspecified dermatitis, dermatitis lichenoid, seborrheic dermatitis)	261	0.2
12	Drug Hypersensitivity Syndrome (DHS)	252	0.2
13	Sweat Gland Disorder (includes decreased sweating, increased sweating, and sweat gland disorder)	193	0.2
14	Purpura (includes purpuric rash)	180	0.2
15	Skin exfoliation	160	0.1
16	Photosensitivity (includes photoallergic reaction, nonspecified photosensitivity, phototoxic reaction)	113	0.1
17	Alopecia	69	0.1
18	Psoriasiform eruptions (includes psoriasiform rash, psoriasis)	66	0.1
19	Skin discoloration (includes skin depigmentation, vitiligo, nonspecified skin discoloration, chloasma, pigmentation abnormal)	56	0.1
20	Acneiform eruptions	29	< 0.1
21	Others	193	0.2

^aTotal number of CADR report included in analysis = 104 372; Number of CADR's frequency > 104 372 as there could be more than one type of CADR reported in a single report.

drugs. Compared to similar studies with smaller sample sizes^{8,11,16} our larger sample size allows for greater power and better capture of the variety of CADR's, specifically the less frequently reported ones.

CADR's are the most commonly reported AEs by organ class, constituting about 60% of all AE reports received by HSA. This is due to CADR's being more visible and easily recognizable, leading to less underreporting as compared to other AEs. The most frequently reported CADR was rashes (inclusive of nonspecified rash, follicular rash, maculopapular rash, vesicular rash) (67.2%), although a large proportion of these were simply reported as "rash". Typically, such rashes are considered nonserious, and hence reported with scanty information. We also received a disproportionately higher number of AE reports for SCAR's compared to other CADR's, suggesting that

TABLE 2 Types of CADR's reported and their frequencies

SCAR cases tend to be reported more conscientiously by health-care professionals, as it is critical to document these in the electronic medical records to prevent reexposure which could be life-threatening.

The top implicated drug classes in our study, namely antimicrobials (43.5%), NSAIDs (16.2%) and analgesics (9.0%) are similar to that reported in an Italian study.⁸ These tend to be associated with nonserious CADR's such as angioedema, urticaria, FDE, and bullous eruption (Table 4). In comparison, a study by Ding et al⁹ focusing on CADR's in a tertiary hospital reported antibiotics, antiepileptics and antigout drugs as the top drug classes implicated, highlighting the difference in the propensity of different drug classes to cause serious CADR's requiring hospitalization.

TABLE 3 Top 10 drug classes reported with CADR, and top five suspected drugs per drug class

No.	Drug classes (ATC Code – Level 2) and suspected drugs	No. of reports	%
1	Antibacterials for systemic use – J01 Amoxicillin Cotrimoxazole Coamoxiclav Benzylpenicillin or Penicillin G Erythromycin	48 874 8511 6921 6609 2787 2714	43.5
2	Antiinflammatory and Antirheumatic products – M01 Ibuprofen Diclofenac Naproxen Mefenamic Acid Etoricoxib	18 265 4185 4006 3234 2922 1214	16.2
3	Analgesics – N02 Paracetamol Tramadol Orphenadrine, Paracetamol Codeine Morphine	10 112 6871 1205 742 566 202	9.0
4	Antithrombotic Agents – B01 Aspirin Clopidogrel Ticlopidine Dipyridamole Warfarin	4353 3915 244 115 47 32	3.9
5	Lipid Modifying Agents – C10 Simvastatin Fenofibrate Lovastatin Atorvastatin Laropiprant and Niacin	2566 1188 472 322 239 100	2.3
6	Contrast Media – V08 Iohexol Ioversol Gadoterate Iopamidol Iopromide	1922 1500 135 65 65 65	1.7
7	Antiepileptics – N03 Phenytoin Carbamazepine Gabapentin Lamotrigine Valproate	1865 697 482 190 174 158	1.6

(Continues)

TABLE 3 (Continued)

No.	Drug classes (ATC Code – Level 2) and suspected drugs	No. of reports	%
8	Drugs for Acid Related Disorders – A02 Omeprazole Famotidine Esomeprazole Ranitidine Magnesium Trisilicate	1578 982 234 95 92 56	1.4
9	Agents acting on the Renin-Angiotensin system – C09 Enalapril Lisinopril Losartan Valsartan Captopril	1438 612 336 335 43 41	1.3
10	Cough and Cold preparations – R05 Dextromethorphan Acetylcysteine Bromhexine Codeine, Ephedrine, Promethazine Codeine, Promethazine	1160 312 242 226 125 88	1.0

4.1 | Selected CADR-of-interest

4.1.1 | Angioedema

Consistent with literature, our results showed that angioedema was commonly caused by NSAIDs, penicillins, and sulfa drugs.^{17,18} While antibiotics-induced angioedema is likely due to type I hypersensitivity, NSAIDs-induced angioedema is considered a nonallergic reaction, attributed to cyclooxygenase (COX) inhibition, leading to the shunting of arachidonic acid toward the production of excessive leukotrienes which are mediators for swelling.^{17,18} This pathophysiology explains why COX-2 inhibitors are better tolerated compared to nonselective NSAIDs, and our study's observation is consistent with this: Angioedema is commonly reported with nonselective NSAIDs (eg diclofenac, ketorolac, etc.), but not so with COX-2 inhibitors (eg etoricoxib) (Table 4). As for paracetamol-induced angioedema, the mechanism is still not well understood, with both IgE-mediated pathway and leukotriene production being possible.¹⁹

4.1.2 | Urticaria

While angioedema is characterized by deep swelling in the submucosal or subcutaneous tissue, urticaria is associated with transient swelling of the skin.²⁰ Drug-induced urticaria can be immunologically mediated (eg with antibiotics), or nonimmunologically mediated (eg with NSAIDs)^{5,21} Our study also observed radiocontrast media, specifically iohexol, as a frequent causative agent for urticaria. It

is postulated that radiocontrast media acts via a nonimmunologic mechanism by triggering direct mast cell degranulation, resulting in histamine release.^{20,21} As such, most cases of symptomatic urticaria can be managed with an antihistamine such as diphenhydramine.²²

4.1.3 | Stevens-Johnson syndrome, toxic epidermal necrolysis (SJS/TEN) and drug hypersensitivity syndrome (DHS)

While SJS/TEN has multiple causes, most are drug-induced,²³ and our study identified antiepileptics (ie carbamazepine, phenytoin, lamotrigine), antibiotics (cotrimoxazole, amoxicillin-clavulanic acid, amoxicillin, ceftriaxone) and allopurinol as commonly implicated drugs (Table 4). A similar drug profile was also seen in our DHS reports, with sulfa-drugs (ie cotrimoxazole, dapson, sulfasalazine) featuring more strongly for DHS. SJS/TEN appear to be more common in females, while the converse is true to DHS. Comparing latency between SJS/TEN and DHS of the top four drugs, latency tends to be longer in DHS than SJS/TEN (median 23 vs 20 days for phenytoin, 28 vs 20 days for allopurinol, 26 vs 7 days for cotrimoxazole and 19 vs 13 days for carbamazepine.)

Human Leukocyte Antigen (HLA) genes have been shown to be associated with drug-induced SCARs, including SJS/TEN due to carbamazepine, phenytoin, and allopurinol.²³ The HLA-B*1502 allele, a well-known marker for carbamazepine (CBZ)-induced SJS/TEN, is present in many Asian populations,^{24,25} including Singapore.²⁶ The frequency for this allele in Singaporeans is approximately 1 in 5 Malays, 1 in 8 Chinese and 1 in 25 Indians, compared to 1 in 500 Japanese or less than 1 in 1000 Caucasians.²⁷ The higher allele frequency in Malays may partly explain the disproportionate number of SJS/TEN cases received: A quarter of the CBZ cases in our study were in Malays, although they comprise only 13.4% of the general population.¹⁶

Between 2003 and 2012, HSA received an average of 15 reports of CBZ-induced SJS/TEN per year. Based on strong data from local and international studies supporting the association between the HLA-B*1502 allele and CBZ-induced SJS/TEN, the Ministry of Health, in a joint Dear Healthcare Professional Letter with HSA issued in April 2013, stated that genotyping of HLA-B*1502 prior to the initiation of CBZ therapy in new patients of Asian ancestry is standard of care.²⁸ This has mitigated the risk of CBZ-induced SJS/TEN locally,²⁹ illustrating the role a regulatory authority can take in advancing the use of pharmacogenetics for drug safety.

For allopurinol, there is a strong genetic association between HLA-B*5801 and allopurinol-induced SCARs. The frequency of this allele in Singaporeans is approximately 1 in 5 Chinese, 1 in 15 Malays and 1 in 25 Indians.³⁰ The higher HLA-B*5801 allele frequency in the Chinese population could partly explain the disproportionately higher number of allopurinol-SJS/TEN cases seen in our study: 85.5% of these occurred in Chinese patients, although the Chinese make up 74.1% of the general population.¹⁶ In contrast to CBZ, a cost effectiveness study found that genotyping all gout patients for the HLA-B*5801 allele prior to initiation of allopurinol is currently

not cost-effective for Singapore's overall population from a health systems perspective. The relatively low positive predictive value of the test and limited alternative urate-lowering therapies were contributory factors to this.³⁰

In the EuroSCAR study, oxicam-NSAIDs (eg piroxicam) were found to be strongly associated with SJS/TEN.²⁹ Conversely, COX-2 inhibitors, celecoxib and rofecoxib, did not show such an association,³⁴ although cases of etoricoxib-induced TEN have been reported.^{32,33} In our setting, systemic oxicam-NSAIDs are not widely used, and we found COX-2 inhibitor etoricoxib as the most frequently reported NSAID associated with SJS/TEN instead.

Sulphonamide antibiotics (eg cotrimoxazole) are well known to cause SJS/TEN, but for amoxicillin and amoxicillin-clavulanic acid, this is less clear. Half of the SJS/TEN reports we received for the drug class penicillins had co-suspected drugs, and in some cases, the antibiotic was started only after the prodromal symptoms of SJS/TEN appeared.

Omeprazole was found to be a co-suspected drug in 60.9% of the omeprazole-SJS/TEN cases, suggesting it could be an innocent bystander. Similarly, in other studies,^{31,34} it was found that pantoprazole was commonly taken with drugs which carry higher risks for SJS/TEN, and was often not temporally convincing. Other proton pump inhibitors (PPIs) have also been reported to carry nonsignificant risk for SJS/TEN.³¹

4.1.4 | Fixed drug eruption (FDE)

Drugs, specifically NSAIDs and antibiotics, are the most common cause of FDEs, and our findings reflect this. Interestingly, a retrospective chart review by the Singapore National Skin Center³⁵ also identified etoricoxib as the most common cause of FDE, accounting for 38.7% of 62 FDE patients. In that study, three-quarters of the patients reacting to etoricoxib were Chinese patients, and this was also observed in our study. The possibility of genetic predisposition was considered, suggesting a genetic association resulting in higher incidence of etoricoxib-induced FDE in the local Chinese population.³⁵

4.1.5 | Acute generalized exanthematous pustulosis (AGEP) and pustular rash

In a EuroSCAR study,³⁶ aminopenicillins, sulphonamides, and quinolones were found to be highly associated with AGEP, but not paracetamol and cephalosporins. In comparison, our results showed that all these drugs were frequently reported to cause AGEP, although in the paracetamol and ceftriaxone cases, one-third were accompanied with co-suspect drugs. While our database did not feature reports of (hydroxy)chloroquine, terbinafine and diltiazem-associated AGEP prominently (≤ 5 reports for each drug), the EuroSCAR study did detect them as culprit drugs which have a high risk of causing AGEP. Different prescribing patterns and under-reporting of AEs could explain this. For similar reasons, we also identified different NSAIDs as causative agents: The EuroSCAR study reported oxicam-NSAIDs, as opposed to diclofenac and ibuprofen seen in our study.

TABLE 4 Ten CADRs-of-interest and their respective top 10 suspected drugs^a

Type of CADRs	No. of suspected drugs	Top 10 suspected drugs (No. of reports of CADR with drug)
Angioedema	17 166	Diclofenac (2159); Paracetamol (1994); Ibuprofen (1797); Naproxen (1555); Aspirin (1474); Mefenamic Acid (839); Cotrimoxazole (584); Amoxicillin (577); Coamoxiclav (420); Ketorolac (322)
Urticaria	8406	Iohexol (652); Coamoxiclav (484); Diclofenac (408); Paracetamol (391); Amoxicillin (352); Aspirin (286); Ibuprofen (259); Ceftriaxone (257); Ciprofloxacin (250); Cotrimoxazole (237)
SJS/TEN	1114	Carbamazepine (126); Cotrimoxazole (84); Allopurinol (80); Phenytoin (53); Omeprazole (46); Coamoxiclav (44); Amoxicillin (41); Etoricoxib (26); Ceftriaxone (24); Lamotrigine (23)
FDE	869	Etoricoxib (95); Cotrimoxazole (94); Paracetamol (67); Doxycycline (47); Coamoxiclav (43); Amoxicillin (29); Tetracycline (27); Ciprofloxacin (23); Mefenamic Acid (19); Diclofenac (15)
AGEP and Pustular Rash	607	Coamoxiclav (69); Amoxicillin (24); Ceftriaxone (24); Cotrimoxazole (24); Clarithromycin (22); Ciprofloxacin (20); Diclofenac (18); Paracetamol (16); Benzylpenicillin/Penicillin G (15); Ibuprofen (15)
Bullous Eruption	562	Cotrimoxazole (56); amoxicillin (26); Tetracycline (26); Coamoxiclav (25); Etoricoxib (24); Paracetamol (18); Diclofenac (17); Doxycycline (16); Aspirin (14); Mefenamic Acid (14)
DHS	325	Allopurinol (57); Phenytoin (39); Cotrimoxazole (33); Carbamazepine (20); Dapsone (14); Sulfasalazine (9); Diclofenac (9); Omeprazole (8); Piperacilin & Tazobactam (7); Vancomycin (6); Coamoxiclav (6); Isoniazid (6); Rifampicin (6)
Photosensitivity	123	Hydrochlorothiazide (37); Doxycycline (10); Fenofibrate (7); Simvastatin (5); Ciprofloxacin (4); Griseofulvin (4); Tetracycline (3); Nifedipine (2); Entecavir (2); Glipizide (2); Hydroxychloroquine (2); Coamoxiclav (2); Amiodarone (2); Atenolol (2); Chlorpromazine (2); Ofloxacin (2)
Alopecia	75	Azathioprine (6); Losartan (5); Leflunomide (5); Amlodipine (4); Atenolol (4); Fluconazole (4); Simvastatin (4); Valproate (3); Nilotinib (3); Acarbose (2); Carbimazole (2); Metformin (2); Imatinib (2); Lisinopril (2); Tolbutamide (2)
Skin Discoloration	62	Simvastatin (5); Cotrimoxazole (5); Amiodarone (2); Laropiprant and Niacin(2); Tetracycline (2); Enalapril (2); Aspirin (2); Ciprofloxacin (2)

^aThe number of drugs involved ≠ number of reports for CADR as more than 1 drug could be suspected in a single report.

4.1.6 | Bullous eruptions

Bullous eruptions encompass a range of clinical presentations such as pemphigus, bullous pemphigoid, and linear IgA bullous dermatosis.^{5,37} Pemphigus can be triggered via a biochemical pathway by thiol drugs (eg d-penicillamine, captopril, lisinopril) or phenol drugs (eg rifampicin, aspirin, levodopa), or via an immune-mediated pathway by non-thiol drugs (eg cephalosporin, penicillin, enalapril), with both pathways leading to acantholysis.³⁷ Bullous pemphigoid, on the other hand, is most often associated with thiol drugs.^{5,37} In linear IgA bullous dermatosis, vancomycin is the most common culprit drug.³⁷ While most of our reports of bullous eruptions did not specify the type of bullous disorder, we did receive reports of vancomycin-associated linear IgA bullous dermatosis, bullous pemphigoid secondary to enalapril, pemphigus vulgaris associated with captopril, as well as with pemphigus with rifampicin.

4.1.7 | Photosensitivity

Drugs often associated with photosensitivity (eg tetracyclines, thiazides, chlorpromazine, amiodarone) were also elucidated by our

study.^{5,38,39} Although entecavir is not known to cause photosensitivity reactions, there were two such reports in our database, one of which was confirmed with skin biopsy showing deep perivascular dermatitis with eosinophils. The elderly patient was on entecavir for 5 months, and recovered 3 months after cessation of drug. Our results also suggest that patients who are female, Chinese or of older age are more likely to develop and report photosensitivity reactions. The protection offered by melanin in darker-skinned patients could explain the higher reporting of photosensitivity reactions by the Chinese.⁴⁰

4.1.8 | Alopecia

Drug-induced alopecia could be categorized into anagen effluvium (ie hair growth phase) or telogen effluvium (ie resting phase).⁴¹ Anagen hair loss is often dose related and commonly associated with chemotherapy, but reports of chemotherapy-induced alopecia are lacking from the AE database. One reason is that expected reactions such as these tend to be under-reported. Telogen hair loss is linked to a wider variety of endogenous and exogenous factors, such as major surgery, serious illness,

TABLE 5 Ten CADR_s-of-interest and their breakdown by demographic characteristics and latency

Type of CADR	Median age (years)	Sex Ratio (M:F)	Race (%)				Median Latency (days)
			Chinese	Malay	Indian	Others	
Angioedema	34 (0-103)	0.82	71.5	13.8	8.1	6.6	0.0
Urticaria	41 (1-101)	0.77	72.3	12.3	7.2	8.2	0.0
SJS/TEN	50 (1-115)	0.89	67.9	19.9	4.9	7.3	12.0
FDE	45.5 (1-93)	1.30	76.1	9.3	9.4	5.2	1.0
AGEP and Pustular Rash	48.5 (1-103)	0.85	67.0	17.0	11.1	5.0	3.0
Bullous Eruption	48.5 (1-96)	1.20	70.9	15.8	7.7	5.6	2.0
DHS	53 (4-89)	1.40	72.9	12.1	7.0	8.0	26.0
Photosensitivity	58 (4-95)	0.65	78.1	12.4	5.7	3.8	31.0
Alopecia	49.5 (11-81)	0.28	75.0	8.9	10.7	5.4	69.5
Skin Discoloration	47 (1-89)	0.46	66.0	8.0	20.0	6.0	4.0
Total	41 (0-115)	0.78	72.5	12.5	8.1	7.0	0.0

Table 5 lists the CADR_s-of-interest from most to least commonly reported. The median age, sex ratio (M:F), racial distribution, and median latency of each CADR is listed.

CADR_s with sex ratio (M:F) greater than one indicate that the CADR is reported more in males than in females, ie FDE, bullous eruption, and DHS. The racial distribution across each CADR was generally consistent with that of the local population [Chinese (74.1%), Malays (13.4%), Indians (9.2%), Others (3.3%)¹⁶], with slight deviations noted for SJS/TEN (more frequently reported in Malays), photosensitivity (more frequently reported in Chinese) and skin discoloration (more frequently reported in Indians).

childbirth, malnutrition, stress, and drugs (eg beta blockers, valproic acid, leflunomide), hence it is more difficult to pinpoint a drug as the causative agent.

Of the six azathioprine reports, four of them were accompanied by pancytopenia or severe neutropenia. Interestingly, in a study on azathioprine side effects in Chinese patients with systemic lupus erythematosus, five out of 126 patients exhibited alopecia, and all five developed leukopenia subsequently. Although it cannot be conclusively said that alopecia and leukopenia are related due to limited data, the study suggested that alopecia could be a sign of hematological toxicity, prompting early reduction or cessation of azathioprine.⁴²

4.1.9 | Skin discoloration

Drugs often implicated in causing skin discoloration are amiodarone, tetracycline, NSAIDs, antimalarials, and psychotropic drugs. Amiodarone is associated with slate-gray pigmentation in unprotected light exposed skin areas, especially in light-skinned individuals on prolonged therapy. This hyperpigmentation is due to the accumulation of amiodarone and its metabolites in the skin.^{43,44} Long term use of tetracyclines are also known to cause abnormal pigmentation. With minocycline, especially when used long term for treatment of acne, pigments are deposited as a result of an insoluble minocycline-melanin complex.⁴⁵ Our study found that females are more likely to report drug-induced skin discoloration. Although Indians make up about 9.2% of the local population,¹⁶ there appears to be a greater proportion of reports of skin discoloration from Indians (20.0%).

5 | CONCLUSION

While our analysis did not detect any new associations or drug signals, it is interesting to note that CADR_s such as SJS/TEN, photosensitivity and skin discoloration seem to be reported more frequently in Malays, Chinese, and Indians, respectively. However, given the limitations of the spontaneous reporting system, these observations should be taken into context. To overcome these limitations, HSA is looking into leveraging on electronic medical records to detect ADRs, including SCARs. With information on race, diagnoses, and medication history, it will become possible to explore the distribution of various CADR_s across different races.

In summary, we have analyzed a large dataset of over 100 000 CADR reports from a 10-year period and identified the types of CADR_s reported, as well as their associated drugs, latency periods, and patient characteristics. Such information could add value to healthcare professionals as they assess CADR cases and evaluate suspected drugs. Timely and accurate identification of the causative drug can enable HCPs to take the appropriate actions and improve patient clinical outcome.

ACKNOWLEDGEMENTS

The authors are grateful for the advice on statistical analysis by Yiong Huak Chan, Head, Biostatistics Unit, Yong Loo Lin School of Medicine, National University of Singapore. We will also like to thank Cheng Leng Chan, Group Director of the Health Products Regulation Group, Dorothy Toh, Assistant Group Director (Vigilance, Compliance & Enforcement Cluster), and Jalene Poh, Director

(Vigilance & Compliance Branch) at the HSA, for their steadfast support to pursue this research to advance the organisation's pharmacovigilance mission.

DISCLOSURE

None declared.

ORCID

Han Hui Cheong  <https://orcid.org/0000-0002-8616-4529>

Sui Yung Chan  <https://orcid.org/0000-0001-5941-6797>

REFERENCES

- World Health Organisation. Technical report no. 498: International drug monitoring: the role of national centres. 1972. Available from <https://www.who-umc.org/media/2680/who-technical-report-498.pdf>. Accessed 17 Sep, 2018.
- Thiessard F, Roux E, Miremont-Salame G, et al. Trends in spontaneous adverse drug reaction reports to the French pharmacovigilance system (1986-2001). *Drug Saf.* 2005;28:731-740.
- Shin YS, Lee YW, Choi YH, et al. Spontaneous reporting of adverse drug events by Korean Regional Pharmacovigilance Centers. *Pharmacoepidemiol Drug Saf.* 2009;18:910-915.
- Aagaard L, Strandell J, Melskens L, Petersen PSG, Hansen EH. Global patterns of adverse drug reactions over a decade analyses of spontaneous reports to VigiBase™. *Drug Saf.* 2012;35:1171-1182.
- Lee A, Thomson J. Chapter 5 Drug-induced skin reactions. In: Lee A, eds. *Adverse Drug Reactions*, 2nd edition. London, United Kingdom: Pharmaceutical Press; 2006:125-156.
- Uppsala Monitoring Centre Annual Report (July 2015 – June 2016). 2018. Available from: https://www.who-umc.org/media/3081/umc-annual-report-final-version_small.pdf. Accessed 17 Sep, 2018.
- VigiBase, Uppsala Monitoring Centre. 2017. Accessed 17 Oct, 2017
- Naldi L, Conforti A, Venegoni M, et al. Cutaneous reactions to drugs. An analysis of spontaneous reports in four Italian regions. *Br J Clin Pharmacol.* 1999;48:839-846.
- Tian XY, Liu B, Shi H, et al. Incidence of adverse cutaneous drug reactions in 22,866 Chinese inpatients: a prospective study. *Arch Dermatol Res.* 2015;307:829-834.
- Lee HY, Tay LK, Thirumoorthy T, Pang SM. Cutaneous adverse drug reactions in hospitalised patients. *Singapore Med J.* 2010;51:767-774.
- Ding WY, Lee CK, Choon SE. Cutaneous adverse drug reactions seen in a tertiary hospital in Johor, Malaysia.. *Int J Dermatol.* 2010;49:834-841.
- Sushma M, Noel MV, Ritika MC, James J, Guido S. Cutaneous adverse drug reactions: a 9-year study from a South Indian hospital. *Pharmacoepidemiol Drug Saf.* 2005;14:567-570.
- Cash TF, Pruzinsky T. *Body Images: Development, Deviance, and Change*. New York: Guilford; 1990.
- Cash TF, Price VH, Savin RC. Psychological effects of androgenetic alopecia on women: comparisons with balding men and with female control subjects. *J Am Acad Dermatol.* 1993;29:568-575.
- Department of Statistics, Ministry of Trade and Industry, Republic of Singapore. Census of Population 2010 Statistical Release 1: Demographic Characteristics, Education, Language and Religion. 2011. Available from: https://www.singstat.gov.sg/-/media/files/publications/cop2010/census_2010_release1/cop2010sr1.pdf. Accessed 17 Sep, 2018.
- Mishra P, Subish P, Bhandari R, et al. Pattern and economic impact of cutaneous adverse drug reactions: initial experiences from the regional pharmacovigilance center, Western Nepal. *Int J Risk Saf Med.* 2006;18:163-171.
- Kaplan AP. Angioedema. *World Allergy Organ J.* 2008;1:103-113.
- Leeyaphan C, Kulthanan K, Jongjareamprasert K, Dhana N. Drug-induced angioedema without urticaria: prevalence and clinical features. *J Eur Acad Dermatol Venereol.* 2010;24:685-691.
- Rutkowski K, Nasser SM, Ewan PW. Paracetamol hypersensitivity: clinical features, mechanism and role of specific IgE. *Int Arch Allergy Immunol.* 2012;159:60-64.
- Tan EKH, Grattan CEH. Drug-induced urticarial. *Expert Opin Drug Saf.* 2004;3:471-484.
- Morzycki A, Bhatia A, Murphy KJ. Adverse reactions to contrast material: a Canadian update. *Can Assoc Radiol J.* 2017;68:187-193.
- Shaath TS, Patel VK, Rajpara AN, Fraga GR, Aires DJ. Chapter 6 Drug-induced urticaria. In: Hall JC, Hall BJ, eds. *Cutaneous Drug Eruptions: Diagnosis, Histopathology and Therapy*. 2015th ed. London: Springer London; 2015:55-63.
- Klimas N, Quintanilla-Dieck J, Vandergriff T. Chapter 24: Stevens-Johnson syndrome and toxic epidermal necrolysis. In: Hall JC, Hall BJ, eds. *Cutaneous Drug Eruptions: Diagnosis, Histopathology and Therapy*. 2015th ed. London: Springer London; 2015:259-269.
- Ferrell PB, McLeod HL. Carbamazepine, HLA-B*1502 and risk of Stevens-Johnson syndrome and toxic epidermal necrolysis: US FDA recommendations. *Pharmacogenomics.* 2008;9:1543-1546.
- Phillips EJ, Chung W, Mockenhaupt M, Roujeau J, Mallal SA. Drug hypersensitivity: pharmacogenetics and clinical syndromes. *J Allergy Clin Immunol.* 2011;127:S60-S66.
- Toh DSL, Tana LL, Aw DCW, et al. Building pharmacogenetics into a pharmacovigilance program in Singapore: using serious skin rash as a pilot study. *Pharmacogenomics J.* 2014;14:316-321.
- Dear Healthcare Professional Letter No. 49: Recommendations for HLA-B*1502 genotype testing prior to initiation of carbamazepine in new patients. Available from <http://www.hsa.gov.sg/DHCPL>. Accessed 17 Sep, 2018
- Product Safety Alert: 29 Aug 2013: Recommendations for HLA-B*1502 genotype testing prior to initiation of carbamazepine in new patients. Available from http://www.hsa.gov.sg/content/hsa/en/Health_Products_Regulation/Safety_Information_and_Product_Recalls/Product_Safety_Alerts/2013/recommendations_for.html. Accessed 17 Sep 2018-
- Adverse Drug Reaction News, Nov 2016, Vol. 18, No. 3. Available from http://www.hsa.gov.sg/content/dam/HSA/HPRG/Safety_Alerts_Product_Recalls_Enforcement/Adverse_Drug_Reaction_News/2016/ADR_News_Dec2016_Vol18_No3.pdf. Accessed 17 Sep, 2018
- Adverse Drug Reaction News, Sep 2016, Vol. 18, No. 2. Available from http://www.hsa.gov.sg/content/dam/HSA/HPRG/Safety_Alerts_Product_Recalls_Enforcement/Adverse_Drug_Reaction_News/2016/ADR_News_Sep2016_Vol18_No2.pdf. Accessed 17 Sep, 2018
- Mockenhaupt M, Viboud C, Dunant A, et al. Stevens-Johnson syndrome and toxic epidermal necrolysis: assessment of medication risks with emphasis on recently marketed drugs. The EuroSCAR-study. *J Invest Dermatol.* 2008;128:35-44.
- Kameshwari J, Devde R. A case report on toxic epidermal necrolysis with etoricoxib. *Indian J Pharmacol.* 2015;47:221.
- Moutran R, Matouk I, Helou J. Etoricoxib-induced toxic epidermal necrolysis. *Int J Dermatol.* 2014;53:275-277.
- Papay J, Yuen N, Powell G, Mockenhaupt M, Bogenrieder T. Spontaneous adverse event reports of Stevens-Johnson syndrome/toxic epidermal necrolysis: detecting associations with medications. *Pharmacoepidemiol Drug Saf.* 2012;21:289-296.
- Heng YK, Yew YW, Lim DSY, Lim YL. An update of fixed drug eruptions in Singapore. *J Eur Acad Dermatol Venereol.* 2015;29:1539-1544.

36. Sidoroff A, Dunant A, Viboud C, et al. Risk factors for acute generalized exanthematous pustulosis (AGEP) - results of a multinational case-control study (EuroSCAR). *Br J Dermatol*. 2007;157:989-996.
37. Stafford MA, Patel SS, Boyers LN, Karimkhani C. Chapter 18 Autoimmune bullous diseases and drugs. In: Hall JC, Hall BJ, eds. *Cutaneous Drug Eruptions: Diagnosis, Histopathology and Therapy*. 2015th ed. London: Springer London; 2015:193-203.
38. Gill L, Lim HW. Chapter 10 Drug-induced photosensitivity. In: Hall JC, Hall BJ, eds. *Cutaneous Drug Eruptions: Diagnosis, Histopathology and Therapy*. 2015th ed. London: Springer London; 2015:107-121.
39. Drucker AM, Rosen CF. Drug-induced photosensitivity: culprit drugs, management and prevention. *Drug Saf*. 2011;34:821-837.
40. Sharma VK, Sahni K. Photodermatoses in the pigmented skin. *Adv Exp Med Biol*. 2017;996:111-122.
41. Lesiak K, Bartlett JR, Frieling GW. Chapter 20 Drug-induced alopecia. In: Hall JC, Hall BJ, eds. *Cutaneous Drug Eruptions: Diagnosis, Histopathology and Therapy*. 2015th ed. London: Springer London; 2015:215-227.
42. Chen Dongying, Lian Fan, Yuan Shiwen, et al. Association of thio-purine methyltransferase status with azathioprine side effects in Chinese patients with systemic lupus erythematosus. *Clin Rheumatol*. 2014;33:499-503.
43. Das S, Kourosh AS. Chapter 9 Pigment changes and drug reactions. In: Hall JC, Hall BJ, eds. *Cutaneous Drug Eruptions: Diagnosis, Histopathology and Therapy*. 2015th ed. London: Springer London; 2015:87-106.
44. Wiper A, Roberts DH, Schmitt M. Amiodarone-induced skin pigmentation: Q-switched laser therapy, an effective treatment option. *Heart*. 2007;93:15.
45. Nisar MS, Iyer K, Brodell RT, Lloyd JR, Shin TM, Ahmad A. Minocycline-induced hyperpigmentation: comparison of 3 Q-switched lasers to reverse its effects. *Clin Cosmet Investig Dermatol* 2013;6:159.

How to cite this article: Wong SX, Tham MY, Goh CL, Cheong HH, Chan SY. Spontaneous cutaneous adverse drug reaction reports—An analysis of a 10-year dataset in Singapore. *Pharmacol Res Perspect*. 2019;e00469. <https://doi.org/10.1002/prp2.469>