

Review Article

Most Common Drug Eruptions by Pattern and Drug Class: A Review

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Abstract

Cutaneous drug reactions come in many different morphologies, distributions and severities ranging from pruritus and erythema to diffuse epidermal denudation requiring hospitalization. The wide variety of presentations and medications responsible make identification and elimination of the offending agent difficult. Here these authors present a review of the common morphologic drug eruptions and their offending drugs.

Keywords: DRESS; Erythema Multiforme; Erythema Nodosum; Lichenoid; Morbilliform; Urticaria, Morphology; Bullous; Erosive; Fixed; Follicular; Pigmentation; Photo; Stevens-Johnsons; Drug Eruption; Sulfonamides; NSAIDs; Anticonvulsants; Monoclonal Antibody

Introduction

There has been an exponential rise in reportable drug eruptions over the last decade [1]. This is partly due to multiple new drug releases, as well as over prescribing of oral antibiotics [2]. Previous reviews have been extremely helpful in providing the necessary information to healthcare professionals. Our goal is to help the practicing clinicians in outpatient and inpatient medicine to determine rapidly by patterns and clinical morphology the associated list of drugs that are implicated in causation.

We have delineated the following morphologic patterns: Acral, bullous, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), erosive, Erythema Multiforme (EM), Erythema Nodosum (EN), Fixed (FD), follicular, hypopigmentation/hyperpigmentation, lichenoid, morbilliform/maculopapular, Photo Drug (PD), pustular, Stevens-Johnson Syndrome (SJS), Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis Overlap (SJS/TEN), Toxic Epidermal Necrolysis (TEN) and urticarial. The clinical descriptions for each morphological drug induced pattern is delineated below in Table 1 [3-25].

What follows is a rapid way to pair a clinical morphology with an associated drug eruption. The chart below will list the drugs most frequently reported in the literature and the chart that follows it represents the compilation of reviews over the last five years of the delineated morphologies and their most commonly associated drugs.

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Morphology	Clinical Characteristics
Acral	Distally distributed eruptions of the hands, feet, nails and ears.
Bullous	Fluid filled blister larger than 1 centimeter.
Drug Rash with Eosinophilia and Systemic Symptoms (DRESS)	Drug reaction with eosinophilia and systemic symptoms mainly appear with an extensive morbilliform rash but can also appear eczematous, pustular, or exfoliative
Erosive	Erythematous sloughing denuded eruption
Erythema Multiforme (EM)	Targetoid annular erythematous macules of varying sizes less than or equal to 1 cm
Erythema Nodosum (EN)	Solitary or multiple erythematous nodules usually localized to extremities
Fixed Drug (FD)	Localized erythematous, usually annular, patch or plaque which can also appear as a solitary bullous eruption
Follicular	Commonly presents as multiple erythematous papules surrounding hair follicles in a truncal pattern, but is not limited to that distribution
Hyperpigmentation	Hyperpigmentation presents as increased pigment such as brown, darker brown, violaceous, salmon-colored, blue-gray, tan, or intense pigmentation such as black coloration
Hypopigmentation	Hypopigmentation presents as diminished pigment presenting either as white or lighter pigmentation
Lichenoid	Usually symmetric, erythematous or violaceous, pruritic papules/plaques on the trunk and extremities
Morbilliform/Maculopapular	Wide-spread truncal erythematous macules and papules
Photo Drug (PD)	Usually striking erythematous macules, patches, papules, plaques distributed in sun exposed areas with sharp cut-offs where clothing abuts via neck, dorsum of hands and forearms
Pustular	Pus-filled papules surrounding hair follicles, but can be non-follicular, in crops
Stevens Johnson Syndrome (SJS)	SJS is sometimes called erythema multiforme major. SJS has multiple erythematous and dusky macules and patches on the trunk, palms and soles with conjunctival erythema or erosions, along with oral, genital, or other mucosal erosions. Often involving 5-10% or more of body surface area
SJS/TEN	Overlap of each morphology above and below
Toxic Epidermal Necrolysis (TEN)	Erythematous or dusky violaceous and erythematous sheets of denuding epidermis often involving greater than 10% body surface area
Urticarial	May appear as erythematous papules or plaques with a wheal-like or erythematous border

Table 1: Morphologies and clinical characteristics [3-11].

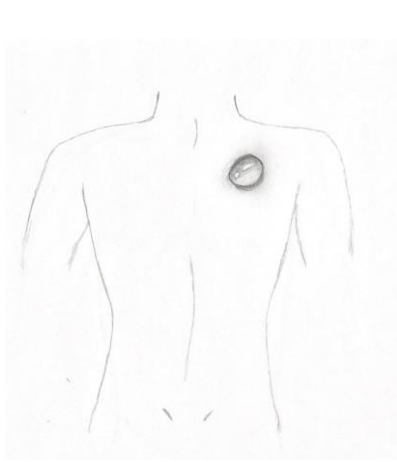
Material and Method

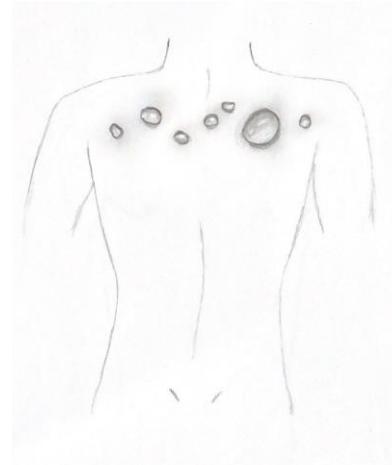
We performed a literature review using PubMed. Thirteen researchers reviewed English, full text, open-access, peer-reviewed meta-analyses, reviews and systematic review articles that were published within the last five years using our specific search terms and inclusion/exclusion criteria. The search was conducted utilizing the morphologic search term and the term “drug eruption” to find and identify the included articles. The title and abstracts were screened for relevance. Articles written prior to five years ago and not in English were excluded. Case reports were excluded due to the lack of quantifiable research. Purpuric drug eruptions were excluded due to the high association with underlying illnesses such as vasculitis. Vaccines were excluded.

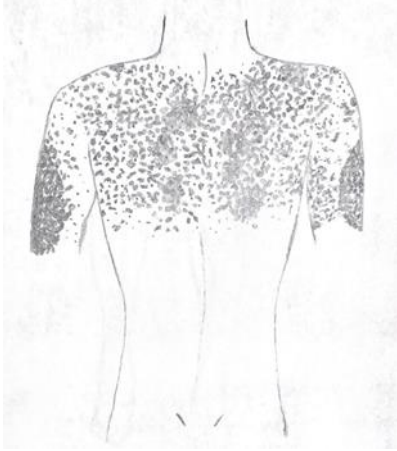
There was a total of 98 articles included and 8 excluded due to containing vaccines as a causative agent. Each article that was identified, was reviewed and data was extracted. This review was conducted from 2 January 2024 through 25 January 2024 [26,27].

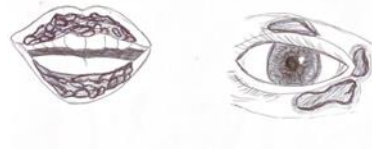
Results

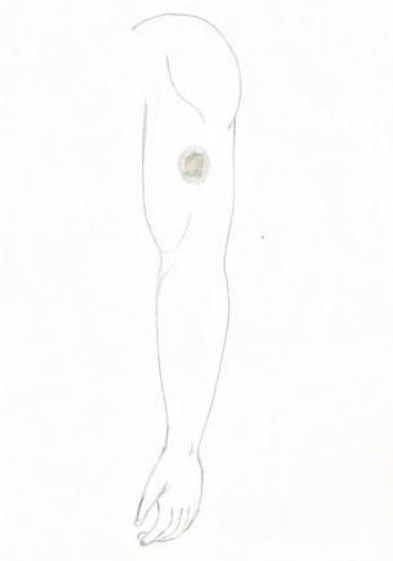
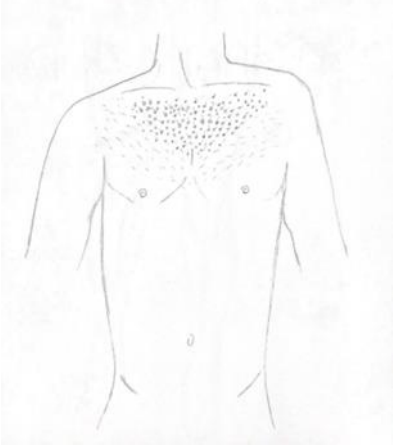
The results include Table 2, Fig.1,2 which are displayed below. Table 2 shows the included drug eruption morphologies with their implicated drug classes and drugs. For better understanding, hand drawn sketches were included in Table 2 to allow the reader to associate the morphology with its appearance. A bar chart (Fig. 1) and pie chart (Fig. 2) are illustrated to represent the patterns found in our research regarding the most offending agents for each morphology and the morphologies that had the most drug classes associated with them [27-104].

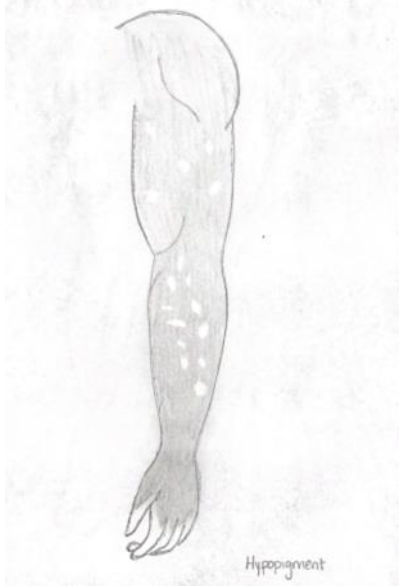
Morphology	Implicated Drug Classes	Commonly Implicated Drugs	Appearance
Acral	- Antineoplastics (Antimicrotubule taxanes, tyrosine kinase inhibitors)	- Docetaxel - Imatinib - Nilotinib	
Bullous	- Analgesics - Angiotensin Converting Enzyme Inhibitors (ACEI) -Angiotensin Receptor Blockers (ARBs) - Antiarrhythmics - Antibiotics (Beta lactams, cephalosporins, nitroimidazoles, quinolones, rifamycins, sulfonamides) - Anticonvulsants - Anti-manics - Antimetabolites	- Acetaminophen - Buprenorphine - Captopril - Candesartan - Amiodarone - Amoxicillin-clavulanate - Amoxicillin - Ampicillin-sulbactam - Ceftriaxone - Cefuroxime axetil - Cotrimoxazole - Metronidazole	

	- Antivirals - Calcium Channel Blockers (CCBs) - Corticosteroids - Cytokines - Disease-Modifying Antirheumatic Drugs (DMARDs) - Granulocyte-Colony Stimulating Factor (G-CSF) inhibitors - Immunosuppressants - Loop Diuretics - Monoclonal Antibodies - Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) - Statins - Sulfonylureas - Tumor Necrosis Factor Inhibitors (TNF) - Xanthine Oxidase Inhibitors	- Moxifloxacin - Penicillin - Piperacillin-tazobactam - Rifampicin - - Trimethoprim-Sulfamethoxazole (TMP-SMX) - Vancomycin - Carbamazepine - Phenytoin - Vigabatrin - Lithium - Gemcitabine - Entecavir - Interferon-α 2a - Amlodipine - Verapamil - Prednisone - Interferon γ / Interleukin 2 - Sulfasalazine - Filgrastim - Cyclosporine - Furosemide - Atezolizumab - Avelumab - Cemiplimab - Durvalumab - Ipilimumab - Nivolumab - Pembrolizumab - Diclofenac - Ketoprofen - Metamizole - Naproxen - Piroxicam - Atorvastatin - Somatostatin - Glibenclamide - Infliximab - Allopurinol	
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Drug Rash with Eosinophilia and Systemic Symptoms (DRESS)	- Antiarrhythmics - Antibiotics (nitroimidazoles, penicillins, sulfonamides) - Anticoagulants - Anticonvulsants - Antidiabetics - Antifungals - Antimalarials - Antituberculars - Antivirals - DMARDs - Erythropoiesis-Stimulating Agents (ESAs) - Histamine antagonist - Monoclonal antibodies - Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) - NSAIDs - Proton Pump Inhibitors (PPIs) - Statins - Tricyclic antidepressants - Tyrosine Kinase Inhibitors - Xanthine Oxidase Inhibitors	- Mexiletine - Amoxicillin - Amoxicillin-clavulanic acid - Ampicillin - Ampicillin/sulbactam - Azithromycin - Benznidazole - Cefadroxil - Cefepime - Cefixime - Cefotaxime - Ceftazidime - Clindamycin - Dapsone - Imipenem - Levofloxacin - Linezolid - Meropenem - Metronidazole - Minocycline - Piperacillin/tazobactam - Streptomycin - Teicoplanin - TMP-SMX - Vancomycin - Rivaroxaban - Carbamazepine - Ethosuximide - Gabapentin - Lamotrigine - Oxcarbazepine - Phenobarbital - Phenytoin - Valproate - Zonisamide - Sitagliptin - Voriconazole - Hydroxychloroquine - Quinine - Ethambutol - Isoniazid - Pyrazinamide - Rifampin - Boceprevir - Telaprevir - Sulfasalazine - Epoetin alfa - Ranitidine	
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		- Daclizumab - Abacavir - Nevirapine - Aspirin - Celecoxib - Diclofenac - Ibuprofen - Piroxicam - Esomeprazole - Omeprazole - Atorvastatin - Amitriptyline - Imatinib - Sorafenib - Vemurafenib - Allopurinol	
Erosive	- Antibiotics (β lactams, cephalosporins, macrolides, quinolones, sulfonamides, tetracyclines) - Anticonvulsants - DMARDs - NNRTIs - NSAIDs - Xanthine Oxidase Inhibitors	- Cotrimoxazole - Carbamazepine - Lamotrigine - Phenobarbital - Phenytoin - Sulfasalazine - Nevirapine - Diclofenac - Meloxicam - Allopurinol	
Erythema Multiforme (EM)	- Angiotensin converting enzyme inhibitors - Antibiotics (β lactams, sulfonamides) - Anticonvulsants - Antifungals - Antimalarials - Antimetabolites - Antineoplastics - Interleukin-6 (IL-6) receptor inhibitor - Monoclonal Antibodies - Mucolytics - NSAIDs - Statins	- Lisinopril - Doxycycline - Carbamazepine - Phenobarbital - Phenytoin - Valproate - Itraconazole - Terbinafine - Hydroxychloroquine - Fluorouracil - Actinomycin D - Paclitaxel - Tocilizumab - Sintilimab - Ambroxol - Bromhexine - Ketoprofen - Naproxen - Phenylbutazone - Pravastatin - Simvastatin	

Erythema Nodosum (EN)	- Angiotensin converting enzyme inhibitors - Antibiotics (aminoglycosides, cephalosporins, sulfonamides) - Anticonvulsants - Antidepressants - Angiotensin receptor blockers - Aromatase Inhibitors - Bromides - Gold Salts - Leukotriene Inhibitors - Oral Contraceptives - PPIs	- Amoxicillin - Ampicillin - Ciprofloxacin - Cotrimoxazole - Minocycline - Nitrofurantoin - Penicillin - Streptomycin - Carbamazepine - Hydantoin - Fluoxetine - Montelukast - Norethindrone - Norgestimate - Levonorgestrel - Omeprazole	
Fixed Drug (FD)	- Antibiotics (Penicillins, Nitroimidazoles, Sulfonamides, Tetracyclines) - Antimalarials - Barbiturates - NSAIDs - Oral Contraceptives	- Amoxicillin - Doxycycline - Metronidazole - Penicillin - TMP-SMX - Quinine - Phenobarbital - Ibuprofen - Celecoxib - Naproxen - Ethinyl estradiol - Medroxyprogesterone acetate - Norethindrone acetate	
Follicular	- Antibiotics (Macrolides, Penicillins) - Anticonvulsants - Antidepressants - Antifungals - Antimalarials - Antimanic - Antipsychotics - Antituberculars - Corticosteroids - Epidermal Growth Factor Receptor Inhibitors - NSAIDs - TNF Inhibitors	- Nystatin - Carbamazepine - Phenytoin - Fluoxetine - Paroxetine - Sertraline - Itraconazole - Hydroxychloroquine - Lithium - Olanzapine - Isoniazid - Corticotropin - Dacomitinib - Gefitinib - Naproxen - Infliximab	

Hyperpigmentation	- Antiarrhythmics - Antibiotics (Tetracyclines) - Anticoagulants - Anticonvulsants - Antimalarials - Antimetabolites - Antimicrobials - Antineoplastics - Antipsychotics - Cytotoxics - Heavy Metals - NRTIs - NSAIDs - Statins - Xanthine Oxidase Inhibitors	- Amiodarone - Minocycline - Carbamazepine - Chlorpromazine - Lamotrigine - Phenytoin - Chloroquine - Hydroxychloroquine - 5-fluorouracil - Clofazimine - Cyclophosphamide - Docetaxel - Doxorubicin - Ifosfamide - Melphalan - Paclitaxel - Thiotepa - Chlorpromazine - Desipramine - Imipramine - Bleomycin - Busulfan - Cyclophosphamide - Gold - Silver - Zidovudine - Aspirin - Ibuprofen - Meloxicam - Paracetamol - Simvastatin - Allopurinol	 Hyperpigment
Hypopigmentation	- Immune Response Modifiers - Monoclonal Antibodies	- Imiquimod - Atezolizumab - Avelumab - Durvalumab - Ipilimumab - Nivolumab - Pembrolizumab	 Hypopigment

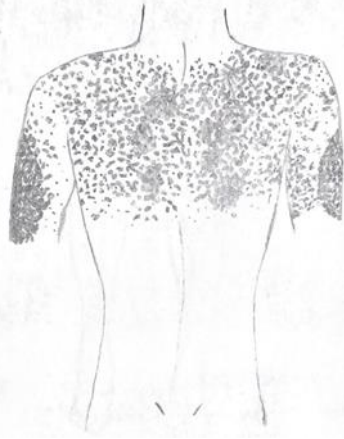
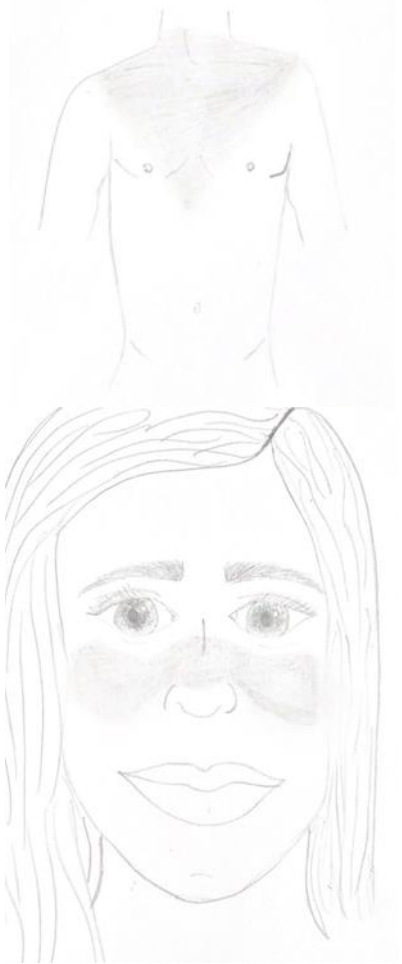
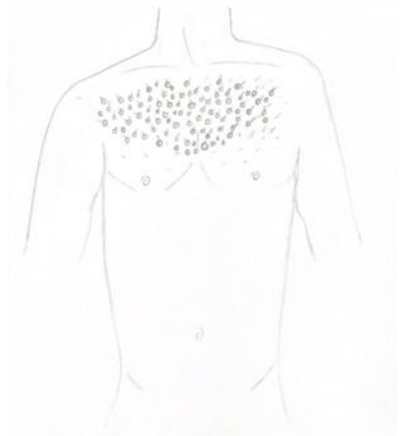
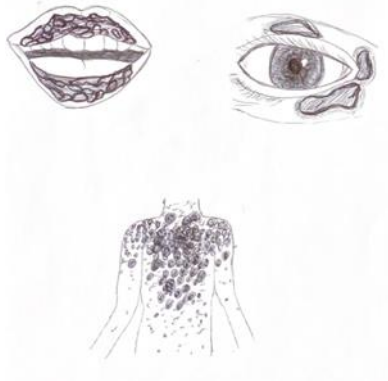
Lichenoid	- Angiotensin converting enzyme inhibitors - Antibiotics - Anticonvulsants - Antihypertensives - Antineoplastics - Antivirals - Calcium Channel Blockers - Diuretics - Monoclonal Antibodies - NSAIDs	- Captopril - Enalapril - Sulfamethoxazole - Carbamazepine - Phenytoin - Methyldopa - Ponatinib - Acyclovir - Nifedipine - Furosemide - Hydrochlorothiazide - Dupilumab - Mogamulizumab - Nivolumab - Rituximab - Ibuprofen - Naproxen	
Morbiliiform/ Maculopapular	- Androgen Receptor Signaling Inhibitors - Antibiotics (Beta lactams, cephalosporins, sulfonamides) - Anticonvulsants - Antimalarials - Antivirals - Monoclonal Antibodies - NSAIDs - Tyrosine Kinase Inhibitors	- Apalutamide - Amoxicillin - Penicillin - TMP-SMX - Carbamazepine - Lamotrigine - Phenobarbital - Phenytoin - Hydroxychloroquine - Dasabuvir - Ombitasvir - Paritaprevir - Simeprevir - Cemiplimab - Daclizumab - Ibalizumab-uk - Ipilimumab - Nivolumab - Pembrolizumab - Siltuximab - Oxicam types (i.e meloxicam) - Fostamatinib	

Photo Drug (PD)	- Angiotensin converting enzyme inhibitors - Antiarrhythmics - Antibiotics (fluoroquinolones, sulfonamides, tetracyclines) - Antifungals - Antimalarials - Antimetabolites - Antineoplastics - Antipsychotics - Antituberculars - Antivirals - CCBs - NNRTIs - NSAIDs - Thiazide diuretics	- Enalapril - Quinapril - Ramipril - Amiodarone - Cefotaxime - Ceftazidime - Dapsone - Doxycycline - Lymecycline - Minocycline - Nalidixic acid - TMP-SMX - Griseofulvin - Itraconazole - Ketoconazole - Terbinafine - Voriconazole - Hydroxychloroquine - Fluorouracil - Paclitaxel - Chlorpromazine - Isoniazid - Pyrazinamide - Sofosbuvir-Velpatasvir - Diltiazem - Efavirenz - Benoxaprofen - Ibuprofen - Ketoprofen - Naproxen - Tiaprofenic acid - Hydrochlorothiazide	
Pustular	- Antibiotics (β-lactams, macrolides, quinolones, sulfonamides) - Antifungals - Antimalarials - CCBs - Tyrosine Kinase Inhibitors	- Amoxicillin - Ampicillin - Pristinamycin - TMP-SMX - Terbinafine - Hydroxychloroquine - Diltiazem - Gefitinib	

Stevens Johnson Syndrome (SJS)	- Antibiotics (β lactams, cephalosporins, fluoroquinolones, sulfonamides) - Anticonvulsants - Antituberculars - DMARDs - Monoclonal antibodies - NRTIs - NSAIDs - Xanthine Oxidase Inhibitors	- Amoxicillin - Azithromycin - Cefotaxime - Doxycycline - Erythromycin - TMP-SMX - Vancomycin - Carbamazepine - Lamotrigine - Levetiracetam - Phenobarbital - Phenytoin - Valproic acid - Isoniazid - Rifampicin - Sulfasalazine - Nivolumab - Pembrolizumab - Abacavir - Nevirapine - Meloxicam - Allopurinol	
SJS/TEN	- Antibiotics (β lactams, cephalosporins, fluoroquinolones, macrolides, sulfonamides, tetracyclines) - Anticonvulsants - Antituberculars - DMARDs - Monoclonal antibodies - NRTIs - NSAIDs - Xanthine Oxidase Inhibitors	- Amoxicillin - Azithromycin - Cefotaxime - Doxycycline - Erythromycin - TMP-SMX - Vancomycin - Carbamazepine - Lamotrigine - Levetiracetam - Phenobarbital - Phenytoin - Valproic acid - Isoniazid - Rifampicin - Sulfasalazine - Nivolumab - Pembrolizumab - Abacavir - Nevirapine - Meloxicam - Allopurinol	See above and below

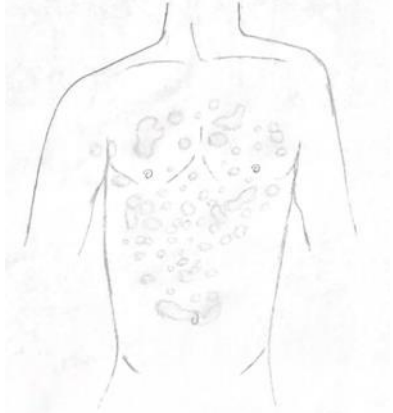
Toxic Epidermal Necrolysis (TEN)	- Antibiotics (fluoroquinolones, sulfonamides, tetracyclines) - Antivirals - Anticonvulsants - DMARDs - NNRTIs - NSAIDs - Xanthine Oxidase Inhibitors	- Cotrimoxazole - Acyclovir - Carbamazepine - Lamotrigine - Phenobarbital - Phenytoin - Sulfasalazine - Nevirapine - Meloxicam - Allopurinol	
Urticarial	- Angiotensin converting enzyme inhibitors - Antibiotics (aminoglycosides, β lactams, cephalosporins, macrolides, penicillins, sulfonamides) - Anticonvulsants - Antifungals - Antimalarials - NSAIDs - Opioids - Oral contraceptives	- Captopril - Lisinopril - Ramipril - Azithromycin - Clarithromycin - Erythromycin - Gentamicin (IV) - Neomycin (topical) - Penicillin - Tobramycin (IV & Inhaled) - Phenytoin - Terbinafine - Hydroxychloroquine - Aspirin - Celecoxib - Diclofenac - Codeine - Morphine - Levonorgestrel - Levonorgestrel/ethinyl estradiol	

Table 2: Categorization of drug eruptions with implicated drug classes and generic drug names with associated morphologic pattern [8-105].

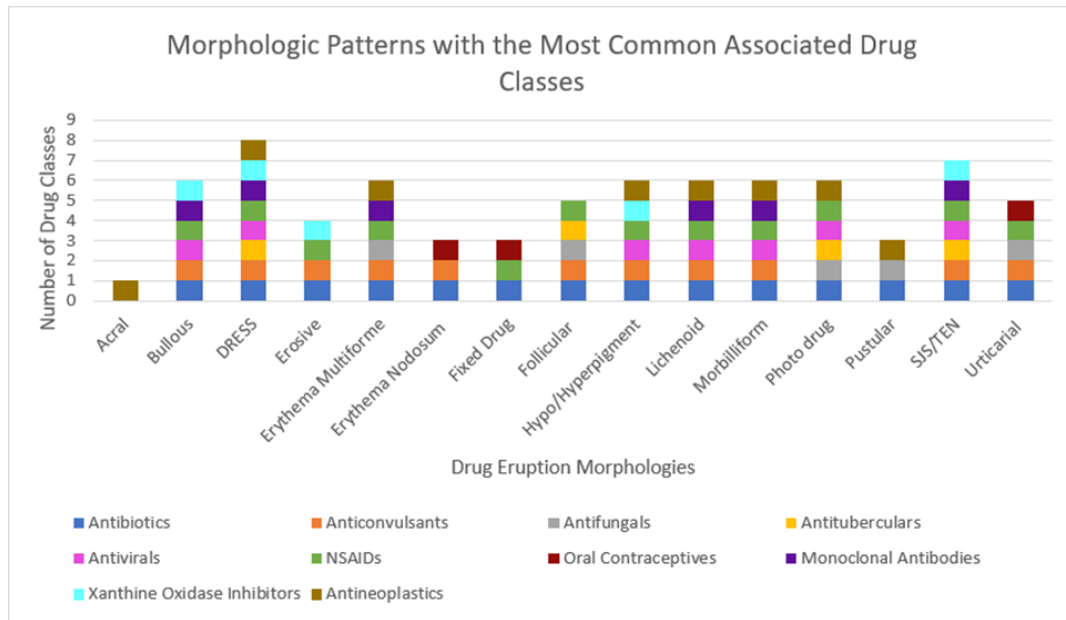


Figure 1: Graphical representation of which drug classes were the most associated with each morphological drug eruption [7-105].

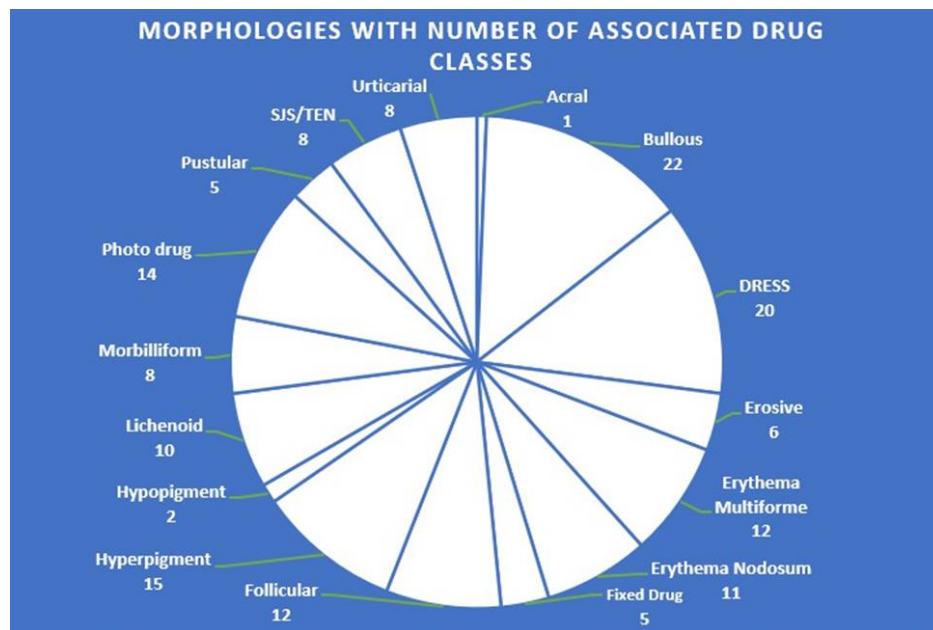


Figure 2: Graphical representation of how many drug classes were associated with each morphological drug eruption [7-105].

Discussion

The morphologies and distributions of these drug eruptions vary significantly (Table 1) but understanding how they present and their cause is crucial for the practicing clinician. Some patients require more medications than others and determining the offending agent amongst a long medication list can be difficult. Discontinuing all medications and reinstituting one medication at a time, to find the offending medication, is not always a reasonable option for patients either. Here is a discussion of each morphology and the most common responsible drugs reviewed in the literature to aid the clinician in identifying the offending agents.

Our research showed that out of the 46 total drug classes, 10 of them were highly associated with most of the morphologies (Fig. 1). These drug classes included antibiotics, anticonvulsants, antifungals, antineoplastics, antituberculars, antivirals, monoclonal

antibodies, NSAIDs, oral contraceptives and xanthine oxidase inhibitors. Once data was compiled, Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), sulfonamide antibiotics and anticonvulsants were the most commonly associated offenders for most morphologies (Table 2). Of all the offending drug classes, antibiotics appeared to be at the top of the list, but strikingly enough, NSAIDs were very close behind.

Interestingly, for the acral drug eruption morphology, there was extreme localization to antineoplastics, specifically antimicrotubule taxanes and tyrosine kinase inhibitors. Bullous drug eruptions have the highest number of implicated drug classes, 22, followed by Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) with 20, hyperpigmentation with 15, photo drug with 14 and erythema multiforme and follicular with 12 (Fig. 2). Specific drugs that were shown to have a high causative association with bullous eruptions included acetaminophen, cotrimoxazole, carbamazepine, metamizole and allopurinol. Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) has the second highest number of implicated drug classes with sulfonamides, anticonvulsants, antituberculars, antivirals and xanthine oxidase inhibitors being the biggest culprits. Erosive drug eruptions had extreme localization to anticonvulsants such as carbamazepine, lamotrigine, phenobarbital and phenytoin. Erythema Multiforme (EM) was closely associated with sulfonamides, anticonvulsants and NSAIDs. Erythema Nodosum (EN) had high associations with antibiotics in the cephalosporin and penicillin classes, as well as oral contraceptives.

Fixed Drug (FD) eruptions were seen to also have close ties with oral contraceptives as causative agents, as well as NSAIDs and sulfonamides like Trimethoprim/Sulfamethoxazole (TMP-SMX). Follicular drug eruptions had 12 associated drug classes with some of the most common contributors being antibiotics, anticonvulsants, antifungals, epidermal growth factor receptor inhibitors and NSAIDs. Hyperpigmentation eruptions were implicated by 14 drug classes and amongst those, amiodarone, minocycline, chlorpromazine, phenytoin, cyclophosphamide, chlorpromazine and allopurinol were the drugs that had the highest association with this eruption. Hypopigmentation eruptions were not found to have many associated drug classes but did have a strong localization to monoclonal antibodies.

Interestingly, lichenoid drug eruptions had many cardiovascular drugs associated with it such as captopril, enalapril, methyldopa, nifedipine, furosemide and hydrochlorothiazide. As well, monoclonal antibodies such as nivolumab and rituximab were strong causative agents. Morbilliform rashes were strongly associated with antibiotics, anticonvulsants, antivirals and monoclonal antibodies, with over 3 implicated drugs in each of those classes. Photo Drug Eruptions (PDE) had solid correlations to tetracyclines, specifically doxycycline, but the most implicated drugs included TMP-SMX, voriconazole, isoniazid, pyrazinamide, efavirenz and naproxen. Pustular drug eruptions were seen to be implicated by 5 drug classes including antibiotics, antifungals, antimalarials, calcium channel blockers and tyrosine kinase inhibitors.

Stevens Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) shared many of the same drug classes and drugs as causative agents, amongst the most popular were antibiotics, specifically TMP-SMX, anticonvulsants such as carbamazepine and lamotrigine, NSAIDs like meloxicam and Xanthine Oxidase Inhibitors such as allopurinol. Urticarial eruptions were strongly associated with antibiotics such as penicillins and sulfonamides. This drug eruption was also seen to be tied to anticonvulsants, antifungals, antimalarials, NSAIDs, opioids and oral contraceptives. There were overlaps in the review between erythema multiforme, SJS and TEN. The reader will realize that there were four groupings associated with these morphologies because in multiple reviews they were separated and in others they were paired. Although this may be a redundancy, this avoids missing important trends in particular manifestations of drug eruptions [104,105]. Over the last five years, many new drugs and drug classes have been introduced which makes it necessary to update correlation between these drugs and drug eruptions by morphology. The reason we associate the morphology with the drug eruption was to help all healthcare providers rapidly correlate clinical situations and determine a shorter list of probable offending agents.

Conclusion

The drugs that appear within this review represent what has been historically documented along with the newer antineoplastic and biologics. We predict that more eruptions will be linked to these classes of drugs as they are increasingly utilized. We believe that these reviews are necessary and should be completed approximately every five years to include new clinical experiences. The trends that we have seen, however, still implicate NSAIDs, antibiotics, specifically sulfonamides and anticonvulsants as the most offending agents.

Conflicts of Interests

The authors declare that there is no conflict of interest for this paper.

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