

Cutaneous Drug Reactions in the Elderly

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Abstract Cutaneous adverse drug reactions comprise a significant proportion of all adverse drug reactions. They may mimic other dermatologic or systemic illnesses and may cause significant morbidity or mortality. Seven morphologic groups encompass the most commonly encountered cutaneous drug reaction syndromes: exanthematous (maculopapular), dermatitic/eczematous, urticarial, pustular, blistering, purpuric, and erythrodermic. Drug reactions may have significant downstream consequences for the older individual.

Key Points

Cutaneous reactions are a significant subset of adverse drug reactions, which can be classified morphologically into seven key groups.

The elderly are at an increased risk for cutaneous adverse drug reactions as a result of comorbidity and polypharmacy.

Cutaneous adverse drug reactions, and sometimes their treatments, have significant and potentially persistent downstream consequences for older individuals likely because of multi-morbidity and the presence of geriatric syndromes.

1 Introduction

1.1 Incidence and Importance of Cutaneous Adverse Drug Reactions in the Elderly

Cutaneous adverse drug reactions (CADRs) comprise a significant proportion of all adverse drug reactions (ADRs). They may mimic other dermatologic or systemic illnesses and must be considered in the differential diagnosis of a broad range of skin conditions. Cutaneous adverse drug reactions themselves may be severe, causing significant morbidity or mortality directly through their effect on the skin. In other cases, they may be the harbinger of significant internal toxicity.

Adverse drug reactions in general are common in the elderly. A recent study estimated that ADRs accounted for 1.5% of emergency hospitalizations among older adults in the USA. Their incidence increased with age, and nearly half of them were among adults 80 years of age or older [1]. The number of diagnoses, number of medications, and the use of medication deemed inappropriate in the elderly are all significantly associated with ADRs in hospitalized elderly patients [2].

The specific incidence of CADRs varies by region and setting. A study in elderly ambulatory patients in the USA found 7.9% of ADRs were classified as dermatologic/allergic [3]. In outpatients in the USA, the incidence of CADRs appears to increase with age, probably peaking in the eighth decade [4]. A Turkish study of elderly patients in an outpatient dermatology clinic found that the incidence of cutaneous drug reactions was 1.4% [5]. In a European study of psychiatric inpatients, monitored over 12 years and including 38,569 patients age 65 years or older, skin eruptions were the second most commonly reported ADR,

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and occurred at a rate of 1.14/1000 patients [6]. A study of intensive care unit patients in Mexico noted an incidence of CADR of 11.6%, and found age over 60 years to be an independent risk factor for CADR [7]. A French study of toxic epidermal necrolysis (TEN) showed increasing incidence with age, peaking in the group aged 75–84 years [8].

Whether age itself is an independent risk factor for CADR is unclear. Many studies do not support this [9–13], though some are suggestive [14]. However, the burden of disease increases with age, and the presence of common chronic conditions in the elderly leads to an increased likelihood of being exposed to medications with the potential for ADRs (Fig. 1 and Table 1) [15]. There are physiologic changes of aging such as reduced renal function and changes in body composition (increased adipose tissue, decreased total body water), which affect the pharmacokinetics of both hydrophilic and lipophilic drugs, and altered drug clearance increases the risk of ADRs in general. The use of multiple medications (i.e. polypharmacy) increases the risk for pharmacokinetic and pharmacodynamic drug interactions [16].

Multi-morbidity, the presence of multiple chronic illnesses, has been shown to correlate with polypharmacy and frailty [17–20]. Frailty is a related concept reflecting aspects of physical aging that may not specifically be due

to disease, such as sarcopenia or decreased gait speed, but which are reflections of declining physiologic reserve [21, 22]. Multi-morbidity and frailty are likely to increase the susceptibility to ADRs as well as the potential for downstream complications and/or poor recovery from ADRs including CADR. These concepts help explain why the older patient develops a disproportionate change in health status from an apparently minor insult. Cutaneous adverse drug reactions may lead to, or exacerbate, other geriatric syndromes, often referred to as the ‘geriatric giants’. For example, pruritus from a drug reaction might exacerbate insomnia and trigger the use of sedating antihistamines leading to falls. Whereas a typical medical disease is defined by a constellation of symptoms, geriatric syndromes are common problems in aging that are better thought of as ‘symptoms’ resulting from a constellation of diseases. The geriatric giants are generally considered to be cognitive decline, mobility decline, incontinence, and frailty [23]. Their significance in the elderly should not be underestimated. Multi-morbidity and frailty are independently associated with worse health outcomes for older individuals such as falls, functional decline, hospitalization, discharge from hospital to an institutional setting, and mortality [18, 24, 25]. Thus, the significance of CADR must be considered in the context of the whole patient.

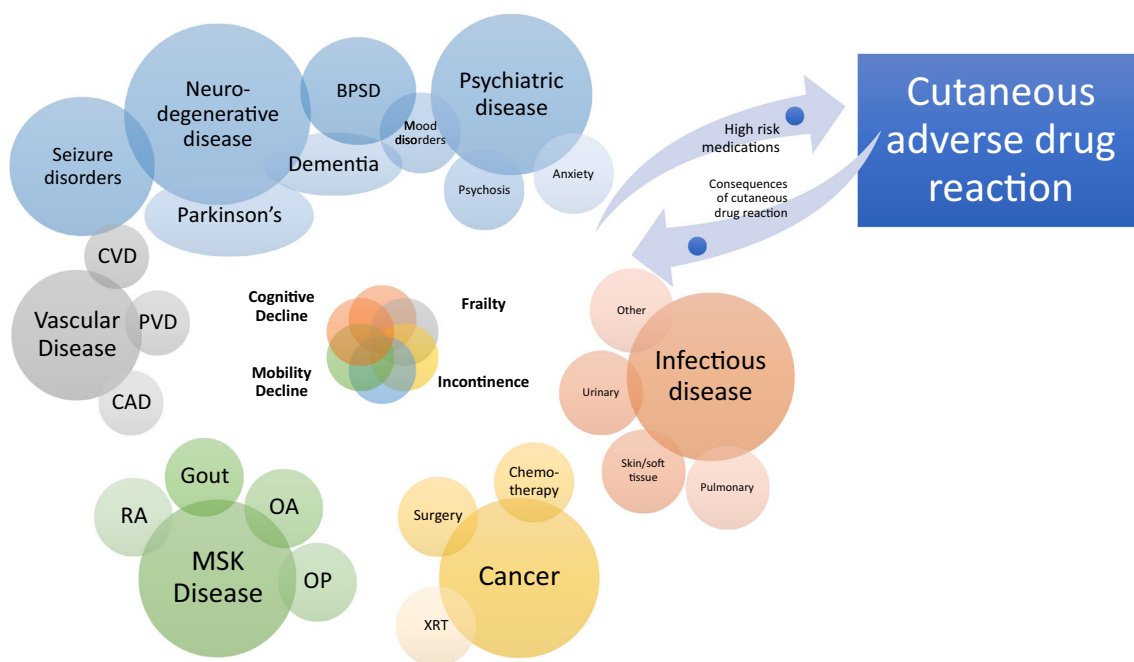


Fig. 1 An increasing burden of interrelated acute and chronic illnesses in the elderly contributes to the development of geriatric syndromes and polypharmacy. This likely increases the risk of developing cutaneous adverse drug reactions. A few representative examples are shown above, though many other diseases would fit into this figure. Importantly, the consequences of cutaneous drug reactions may directly impact health/functional abilities or necessitate drug

therapy, which can exacerbate medical conditions or geriatric syndromes, potentially leading to a cascading failure of health status and physical function. *BPSD* behavioral and psychiatric symptoms of dementia, *CAD* coronary artery disease, *CVD* cerebrovascular disease, *MSK* musculoskeletal, *OA* osteoarthritis, *OP* osteoporosis, *PVD* peripheral vascular disease, *RA* rheumatoid arthritis, *XRT* radiation therapy

1.2 Assessment, Diagnosis, and Pathogenesis

From the mechanistic perspective, ADRs in general are characterized as either ‘type A’ (predictable, related to the drug mechanism; 80–90% of all ADRs) or type B (idiosyncratic, immunologic, unrelated to the drug mechanism; 10–20% of all ADRs) (Table 2). Cutaneous adverse drug reactions can further be classified by their specific mechanism. The most severe drug reactions are type B immunologic CADRs, owing to T cell-mediated type IV hypersensitivity reactions, and can be caused by a variety of commonly used drugs (Table 1). However, from the clinical perspective these categorizations are unhelpful in approaching the undifferentiated rash. A more clinically useful approach is to first classify a rash based on its morphology. This also keeps the differential diagnosis broad, which is important because dermatologic conditions unrelated to drug toxicity may present similarly.

Seven morphologic groups describe the most commonly encountered CADR syndromes: exanthematous (maculopapular), dermatitic/eczematous, urticarial, pustular, blistering, purpuric, and erythrodermic (Table 3). The most common cutaneous drug reactions are exanthematous, dermatitic, and urticarial. Rare but more serious are blistering, pustular, erythrodermic and purpuric eruptions. After characterizing the rash morphologically, the underlying reaction-type/syndrome can be narrowed down and culprit drugs further considered. Another important feature to establish is whether the reaction is limited to the skin, or whether there is systemic involvement. General steps in the approach to cutaneous drug reactions have been previously outlined [26]. Scoring systems also exist to establish drug causality in specific syndromes, for example, the algorithm of drug causality in epidermal necrolysis (ALDEN) score in Stevens–Johnson syndrome (SJS)/TEN [27].

Table 1 Commonly used medications in the elderly most often implicated in severe cutaneous adverse drug reactions

Drug class	Drug	DRESS [28, 29]	SJS/TEN [27, 30, 31]	AGEP [29, 32]
Antibiotics	Aminopenicillins	✓	✓	✓✓
	Cephalosporins	✓	✓	✓
	Sulfonamides	✓	✓✓	✓✓
	Fluoroquinolones		✓	✓✓
	Glycopeptides	✓		
	Macrolides		✓	✓
	Imidazole antifungals		✓	
	Terbinafine			✓✓
Anticonvulsants	Carbamazepine	✓✓	✓✓	✓
	Oxcarbazepine	✓	✓	
	Lamotrigine	✓	✓	✓
	Phenytoin	✓	✓✓	✓
	Primidone	✓	✓	
	Phenobarbital	✓	✓✓	✓
Antidepressants	Sertraline		✓	
Antipsychotics	Olanzapine	✓		
Gout treatment	Allopurinol	✓✓	✓✓	
Cardiac drugs	Diltiazem			✓✓
DMARDs	Sulfasalazine	✓	✓	
	Hydroxychloroquine			✓✓
NSAIDs	Acetic acid derivatives		✓	
	Propionic acid derivatives		✓	
	Enolic acid derivatives (oxicams)	✓	✓✓	✓

The drugs associated with other cutaneous reactions, such as generalized bullous fixed drug eruptions, drug-induced bullous pemphigoid, drug-induced pemphigus, linear immunoglobulin A bullous dermatosis, and drug-induced cutaneous lupus, are not well defined in terms of their specific risk. Owing to the rarity of those conditions, associations are mostly confined to case reports and case series

AGEP acute generalized erythematous pustulosis, DMARD disease-modifying anti-rheumatic drug, DRESS drug reaction with eosinophilia and systemic symptoms, NSAID non-steroidal anti-inflammatory drug, SJS Stevens–Johnson syndrome, TEN toxic epidermal necrolysis, ✓ 1–15%, or established association, ✓✓ 15% or higher, or particularly high risk

Table 2 Immunologic [33] and non-immunologic mechanisms of cutaneous drug reactions

Type	Mechanism	Example
Non-immunologic (type A, predictable)		
Pharmacologic side effect	Unwanted but expected effect of drug-receptor interaction at off-target sites	Anticholinergic use causing dry skin because of reduced perspiration
Secondary to pharmacologic side effect	Altered local immune function?	Cellulitis due to denosumab
Drug-drug interaction	Pharmacokinetic drug interaction increases drug concentrations, leading to dose-dependent side effects	Clarithromycin use increases simvastatin levels via CYP3A4 inhibition leading to statin-related dermatitis
Direct drug toxicity	Expected effect of drug-receptor interaction at target sites	Erlotinib-induced folliculitis owing to EGFR inhibition
Indirect effect	Photoactivation of drug releases toxic mediators that directly damage skin	Phototoxic rash from fluoroquinolone
Immunologic (type B, idiosyncratic/unpredictable)		
Type I	IgE mediated	Anaphylaxis to penicillin
Type II	Antibody-mediated cytotoxicity	Purpura due to HIT
Type III	Immune complex mediated	Serum sickness, hypersensitivity vasculitis
Type IV	Delayed, T cell-mediated activation of effector cells	Simple exanthems, DRESS, AGEP, SJS/TEN
Type IVa	Activation of macrophages	Allergic contact dermatitis due to rivastigmine patch
Type IVb	Activation of eosinophils	Maculopapular drug eruption, DRESS
Type IVc	Activation of cytotoxic T cells	SJS/TEN
Type IVd	Activation of neutrophils	AGEP
Unclassified		Drug-induced lupus
Unclassified		Fixed drug eruption
Antibody mediated	Antibody formation stimulated by non-thiol non-phenol	Drug-induced pemphigus due to NSAID
Cytokine mediated	Cytokine induction by phenols	Drug-induced pemphigus due to levodopa
Idiosyncratic	Direct keratinocyte acantholysis by thiols	Drug-induced pemphigus due to captopril
Photoallergic	Photoactivation of drug leads to release of immunogenic metabolites and allergic response	Photoallergic reaction to quinidine
Pseudoallergic	Direct release of mast cell mediators	Anaphylactoid reaction to radiocontrast media

AGEP acute generalized erythematous pustulosis, *CYP* cytochrome P450, *DRESS* drug-reaction with eosinophilia and systemic symptoms, *EGFR* epidermal growth factor receptor, *HIT* heparin-induced thrombocytopenia, *IgE* immunoglobulin E, *NSAID* non-steroidal anti-inflammatory drug, *SJS/TEN* Stevens–Johnson syndrome/toxic epidermal necrolysis

Table 3 Morphologic classification of drug-induced rashes encountered in the elderly

	Exanthematous	Dermatitic	Urticarial	Pustular	Blistering	Purpuric
Commonly associated eruptions	1. Simple exanthems (e.g., maculopapular rash) 2. Complex exanthems (e.g., DRESS)	1. Phototoxic reaction 2. Photoallergic reaction 3. Primary dermatitic reaction 4. Drug-induced xerosis	1. Anaphylactic 2. Anaphylactoid 3. ASA associated 4. Angioedema 5. Urticarial vasculitis 6. Serum-sickness-like reaction	1. AGEP 2. DRESS	1. Fixed drug eruption 2. SJS/TEN 3. Drug-induced pemphigus 4. Drug-induced bullous pemphigoid 5. Pseudoporphyria 6. Drug-induced linear IgA bullous dermatosis	1. Drug-induced vasculitis 2. Warfarin-induced skin necrosis 3. Heparin-induced skin necrosis

AGEP acute generalized erythematous pustulosis, *ASA* acetylsalicylic acid, *DRESS* drug-reaction with eosinophilia and systemic symptoms, *IgA* immunoglobulin A, *SJS/TEN* Stevens–Johnson syndrome/toxic epidermal necrolysis

2 Common Cutaneous Adverse Drug Reactions

2.1 Simple Exanthems

Exanthematous eruptions are the most common type of CADR, accounting for as many as 95% of reactions, though incidence figures vary considerably. Figures for incidence by age are difficult to come by and it is not clear if they are more common in the elderly, though they remain one of the most common reactions [34]. Exanthems consist of small fixed erythematous spots that blanch with pressure. They may be slightly papular but do not blister or form pustules. Terms such as morbilliform, scarlatiniform, and roseolar-like may be used to describe them because they may resemble viral exanthems. Exanthems may be simple or complex.

Simple exanthems by definition do not involve internal organs or ulceration of mucosal surfaces. They typically begin 5–14 days after drug initiation, occasionally even after the drug is stopped. Discontinuation of the offending medication is typically all that is required for resolution of the rash, which may first desquamate or show transient pigmentary changes. Emollients, topical corticosteroids, or systemic antihistamines may alleviate pruritus, which may be present. However, given the benign nature of these reactions, antihistamines for symptom relief should be used judiciously, as they may be sedating or have other adverse effects (Table 4). Comorbidities, especially those which directly impact the immune system, such as human immunodeficiency virus infection or stem-cell transplant, may increase the risk for exanthematous eruptions [12, 35, 36]. Concurrent medications may also influence risk. For example, allopurinol use may increase the risk of antibiotic-associated exanthematous eruptions [37]. Most simple exanthems do not have the potential to become more severe.

However, severe reactions such as drug reaction with eosinophilia and systemic symptoms (DRESS) and SJS/TEN occasionally resemble simple exanthems in their earliest stages. Larger coalescing macules with a gray or violaceous appearance should raise concern that a more severe reaction is occurring. Similarly, other red flags are the presence of fever above 38.5 °C, lymphadenopathy, mucous membrane involvement, or facial edema/erythema [36]. Simple exanthems should be monitored for resolution to avoid missing serious reactions.

2.2 Dermatitis

Nuisance skin reactions occur commonly in the elderly, with pruritus being the most common complaint [40]. Dermatitis, eczematous rashes, and pruritus are common

drug-related cutaneous reactions that can occur through a variety of mechanisms. Drugs may deplete skin lipids, which perform barrier functions in normal skin, or skin water content, making skin more susceptible to irritation. Aged skin already tends to be thinner and dryer because of atrophy and reduced glandular secretions [41, 42]. Other drugs may directly release inflammatory mediators. Some drugs result in photosensitivity.

Cholesterol and other lipids are important in skin barrier functions and the use of statins can disturb this function causing dry skin and eczema [43]. Spironolactone reduces sebum production [44]. Diuretics in general may reduce skin water content. Anticholinergic drugs contribute to skin dryness by reducing perspiration. Dry skin may be asymptomatic but can lead to pruritus or asteatotic dermatitis or eczema. Opioids can cause intense pruritus as a result of the direct release of histamine. These effects are at least partly owing to the dose/potency of the opioids used. Antihistamines may be useful to treat this side effect, though both opioids and antihistamines have the potential to provoke confusion or delirium [45].

The prevalence of allergic contact dermatitis may be higher in the elderly [46, 47], though conflicting data exist [48]. Allergic contact dermatitis appears to be more common in people with venous stasis ulcers of the legs [49], a common problem in the elderly. The sensitivity is usually to some component of a topical therapy applied to the ulcer, or to the compression garments [50] applied. Patch testing is the usual method for diagnosis, and many topical products cause delayed reactions, meaning delayed readings should be taken at 7–10 days [51]. Older patients may need assistance removing the patches because of limited shoulder mobility.

Cholinesterase inhibitors are indicated for the treatment of some dementias. The incidence of dermatologic adverse events is fairly low (1–3% or lower) and generally similar to placebo in clinical trials with the oral cholinesterase inhibitors, though rare severe reactions are reported. However, the cholinesterase inhibitor rivastigmine is also available in a transdermal patch formulation. The transdermal rivastigmine patch may cause dermatitis. In the IDEAL trial, 7.6% of patients reported a moderate or severe reaction, and in 2.5% of patients skin reaction was the reason for medication discontinuation [52]. As with most medical patches, the most common reaction is an irritant dermatitis. Irritant contact dermatitis is caused by direct skin injury, with or without skin inflammation. It appears as well-demarcated erythema of the exposed skin, and may be associated with mild pain or pruritus. The presence of vesicles, edema, and extension of rash beyond the patch borders suggests allergic dermatitis. Resolution after removal of the patch is generally adequate to confirm

Table 4 Possible treatments for cutaneous drug reactions

Drug class	Drugs	Mechanism of side effects	Possible side effects	Anticholinergic risk score [38] (if applicable)	Potential for sedation [39] (PIR ^a) [if applicable]
First-generation histamine H ₁ antagonists	a. Chlorpheniramine	Antihistaminergic, anticholinergic, off-target effects (α -adrenergic antagonism, serotonergic effects)	Delirium, cognitive adverse effects, urinary retention, constipation	a. +++	a. 1.956
	b. Diphenhydramine			b. +++	b. 1.616
	c. Hydroxyzine			c. +++	c. 2.104
	d. Dimenhydrinate			d. +++	d. 1.369
Second-generation H ₁ antagonists	a. Loratadine	Antihistaminergic, anticholinergic	Delirium, cognitive adverse effects	a. +/++	a. 0.357
	b. Desloratadine			b. +	b. 0.140
	c. Cetirizine			c. +/++	c. 0.193
	d. Levocetirizine			d. +	d. 0.00
	e. Fexofenadine			e. ++	e. 0.021
Other H ₁ antagonists	a. Doxepin (tricyclic antidepressant sometimes used for its antihistamine effects)	Antihistaminergic, anticholinergic, α -adrenergic antagonism	Delirium, cognitive adverse effects, urinary retention, constipation, postural hypotension	a. +++	
H ₂ antagonists	a. Ranitidine	Antihistaminergic, anticholinergic	Delirium, cognitive adverse effects	a. +/++	
	b. Cimetidine			b. +/++	
	c. Nizatidine			c. +	
Systemic corticosteroids	a. Hydrocortisone	Glucocorticoid, anticholinergic	Delirium, psychosis, accelerated bone loss, proximal myopathy, gastric ulceration, insomnia, diabetes, fluid retention/congestive heart failure, opportunistic infections, skin atrophy, secondary adrenal insufficiency	a. +	
	b. Prednisone			b. +	
	c. Methylprednisolone			c. +	
	d. Triamcinolone			d. +	
Topical corticosteroids	Numerous	Glucocorticoid	Skin atrophy, systemic effects		

Many of these agents have risks that are especially significant in the elderly. Anticholinergic activity increases the risk for confusion, sedation, and other anticholinergic adverse events (+ low, ++ intermediate, +++ high)

^a PIR is the overall proportional impairment ratio; a composite score of subjective and objective measures of sedation; higher numbers are indicative of greater potential for sedation

the diagnosis. If the reaction does not resolve within 1 week, suspicion for an allergic reaction increases [53].

Some drug reactions are influenced by exposure to light and these can be characterized as either phototoxic or photoallergic drug reactions [54]. It is unclear whether their incidence differs in the elderly. Phototoxic reactions are more common and resemble sunburn [55]. Phototoxic reactions occur when ultraviolet light directly reacts with the drug to release toxic mediators that damage the skin. They exist on a spectrum through localized photodistributed tender erythema to blistering and hyperpigmentation. Phototoxic reactions may occur at any point after the ingestion of a culprit drug where sufficient sun exposure occurs. Photoallergic eruptions may be exanthematous, dermatitis, or lichenoid and can be pruritic [26]. Because of

their allergic nature, photoallergic reactions require a typically require a sensitization period of several days [56]. In photoallergic reactions, ultraviolet light likely interacts with a drug to produce an immunoreactive byproduct, which then triggers the allergic response. The differential includes conditions that may generate rash in a potentially sun-exposed area such as lupus, or dermatomyositis. Photopatch testing may be required for diagnosis. Resolution of the rash may take weeks or occasionally months. Patients may rarely develop a persistent photosensitivity [56, 57].

The incidence of most malignancies steadily rises with age [58]. A host of new targeted agents for the treatment of various cancers have been brought to market in the last decade. Small-molecule kinase inhibitors cause a multitude

of cutaneous reactions, including dermatitis, xerosis, hair and nail changes, pigmentary changes, and hand-foot syndrome [59–62]. Interestingly, rash development correlates positively with response to therapy in some cases. Immune checkpoint inhibitors appear to be the next wave in oncology and have their own dermatologic effects [63]. A discussion of these agents is largely beyond the scope of this review. To provide a few examples, epidermal growth factor receptor inhibitors, used in lung, breast, and colon cancer, may be associated with phototoxic or photoallergic reactions [64]. BRAF inhibitors, such as vemurafenib, used for the treatment of some metastatic melanomas cause phototoxic reactions commonly [65, 66]. Denosumab, a monoclonal antibody inhibitor of the receptor-activator of nuclear factor-kappa B ligand (RANKL), is used in high doses to prevent skeletal metastases in patients with certain cancers, and also in low doses in the management of osteoporosis. Interestingly, in the FREEDOM trial of denosumab (mean age 72 years), there was a slightly higher incidence of eczema and cellulitis, suggesting that RANKL inhibition may influence skin inflammation or immune tolerance in some situations [67].

2.3 Urticaria

Drug-induced urticaria is clinically and mechanistically heterogeneous. Classically urticarial lesions are hives, raised wheals with unusual shapes that migrate, and are intensely itchy. Involvement of the deep dermis and subcutaneous tissues may lead to angioedema, which may involve the lips, eyelids, or tongue, and can be life-threatening if the airway is compromised. Urticaria may accompany anaphylaxis and occur within minutes of exposure to an allergen. Antibiotics are the most common cause of fatal anaphylaxis [68], and skin testing can confirm an allergy. Anaphylactoid reactions are not true anaphylaxis but can be clinically indistinguishable from anaphylaxis because they also result in the rapid release of mast cell mediators.

The incidence of anaphylaxis may decrease gradually with age [69]. However, rates of drug-induced anaphylaxis, and fatalities from anaphylaxis increase steadily with age [68, 70]. Individuals with established cardiovascular disease are at a higher risk of developing severe or fatal anaphylaxis, and the use of angiotensin converting enzyme inhibitors and β -blockers may increase the severity or make it harder to treat [71]. The injection of epinephrine is life saving. There are no absolute contraindications to its use, even in the case of known cardiovascular disease. There appears to be a reluctance to treat older people for fear of adverse cardiovascular outcomes, but this is overstated and most older patients should receive epinephrine, preferably by the intramuscular route [72]. Intravenous

administration is clearly associated with a greater risk of cardiovascular complications in both younger and older patients, compared with intramuscular injection [72, 73].

Urticaria due to non-steroidal anti-inflammatory drugs (NSAIDs) or acetylsalicylic acid (ASA) may occur minutes to days after initiation. Multiple reactions subtypes are well described, either pseudoallergic or allergic, and can be accompanied by respiratory symptoms or even anaphylaxis [74]. Angioedema due to angiotensin converting enzyme inhibitors appears to have a rather unpredictable temporal course, with some cases occurring early, and others years after drug initiation [75]. Drug-associated urticaria usually fluctuates but settles gradually over hours to weeks after drug cessation. Persistence longer than this should prompt consideration of other causes. Subacute and chronic urticarial reactions can be managed with antihistamines. Newer generation non-sedating antihistamines are preferable to avoid cognitive adverse effects in the elderly (Table 4).

Urticarial lesions that remain fixed in location for 24 h or longer suggest urticarial vasculitis or a serum sickness-like reaction [76]. Serum sickness-like reactions resemble true serum sickness but are not due to the administration of autologous serum. Fever, arthralgia, and rash (usually urticarial) occur 1–3 weeks into drug therapy. Lymphadenopathy and eosinophilia may occur. Fortunately, serum sickness-like reactions are not the result of immune complex formation and thus the more severe sequelae of serum sickness, such as vasculitis, nephritis, and endocarditis, are not seen. Complement levels should be checked in urticarial vasculitis because urticarial vasculitis can be subdivided into two types based on a normal or low complement. Hypocomplementemia is associated with underlying connective tissue disease rather than drug-related causes, and more extensive vasculitis with internal organ involvement [76]. Drug cessation and symptomatic treatment (antihistamines, topical corticosteroids, antipyretics) are typically all that is required, but occasionally a short course of oral corticosteroids may be needed.

3 Uncommon and Severe Cutaneous Adverse Drug Reactions

3.1 Drug Reaction with Eosinophilia and Systemic Symptoms and Erythroderma

Exanthems accompanied by fever and internal organ involvement are characterized as ‘complex’. Generally, this occurs as DRESS. DRESS is often delayed, occurring 1–6 weeks, or occasionally 2–3 months, after drug initiation. It may present with a prodrome that mimics a viral

upper-respiratory tract infection, with fever, malaise, and pharyngitis, followed by rash in 85% of patients. Lymphadenopathy, hematologic abnormalities, and hepatitis are common. In the elderly, comorbidities or unrelated drugs may contribute to evidence of internal organ dysfunction, for example, abnormal laboratory values related to hepatic or renal function. The DRESS diagnostic criteria must be applied carefully to avoid misdiagnosis when these concurrent issues are present.

With DRESS, the two key threats to the patient are the severity of internal organ damage, and the severity of the rash itself. Massive hepatic necrosis, pneumonitis, renal failure, carditis, or colitis may lead to death. Older age appears to be a risk factor for end-organ complications and more severe disease [77, 78]. DRESS may occasionally present with pustules, which are follicular in location, which helps differentiate them from the pustules of acute generalized exanthematous pustulosis (AGEP) [28]. The rash may remain exanthematous but all other common rash morphologies have been described in DRESS. It can evolve to more severe phenotypes of erythroderma or blistering, thus increasing the severity of the overall syndrome. The mortality rate for DRESS may be 10–20%, frequently owing to hepatic failure.

Drug-induced erythroderma is characterized by widespread confluent skin erythema with scaling and serous exudate. After pre-existing skin conditions, drugs are a distant second as the next most common cause of erythroderma [79–83]. Erythroderma seems to occur more commonly in middle age, between approximately 40 and 60 years [79, 80, 83, 84]. By definition, it involves 90% or more of the body-surface area. It is more often seen as a complication of DRESS or AGEP, thus the presence or absence of other features such as blisters or pustules, as well as internal organ involvement, further subdivides the causes of erythroderma. The generalized rash that is seen in SJS/TEN is not a strict erythroderma, but could be misinterpreted as such by the non-expert. The presence of severe mucositis in this situation should raise concern for SJS/TEN.

In the elderly, hospital admission is required owing to the risk of significant morbidity/mortality. Erythroderma and fever may place significant demands on the cardiorespiratory system, leading to high-output cardiac failure [85, 86]. Topical corticosteroids may provide symptomatic relief but also aid vasoconstriction, which may lessen the cardiovascular demands of increased skin perfusion. The increased metabolic rate contributes to a catabolic state with hypoalbuminemia, edema, and muscle loss, a particular concern in the elderly because recovery from such a state is likely to be protracted. Drug-induced cases may actually have a higher likelihood of clearing [84]. At least one study has suggested that erythroderma

has lingering effects on survival beyond the initial episode, and patients in this study had an older mean age (61 years) [82].

3.2 Blistering Reactions

3.2.1 Fixed Drug Eruptions

Fixed drug eruptions (FDEs) characteristically recur in a specific location upon rechallenge with the offending medication. The acute FDE occurs as a single or small number of round-to-oval, red-to-violaceous plaques, usually on the lips, genital/perianal regions, hands, or feet. Lesions resolve with post-inflammatory hyperpigmentation with a gray/brown appearance. Lesions occasionally blister centrally. After one or more local occurrences, FDEs can occasionally evolve into a generalized bullous form (GBFDE), which may mimic SJS/TEN, though the two are usually histopathologically distinct [87, 88]. A GBFDE affects mainly older individuals. A GBFDE usually has minimal or no mucosal involvement, which differentiates it from SJS/TEN. While a GBFDE has traditionally been viewed as more benign than SJS/TEN, a case-control study comparing patients with GBFDEs (median age 78 years) to patients with SJS/TEN showed that GBFDE had a 22% mortality rate, which was only slightly (but not statistically significantly) lower than that of SJS/TEN (28% mortality) [89]. The authors concluded that severe GBFDE cases deserve the same level of care and active management as SJS/TEN. In this study, death from GBFDE occurred exclusively in patients aged 60 years or older.

3.2.2 Drug-Induced Pemphigus

In all new cases of pemphigus in the elderly, drugs should be considered as a cause, although overall drug-induced pemphigus is rare. Occasionally, a very long latency between drug use and onset of pemphigus may be seen, sometimes 6 months or longer, thus a detailed drug history over the previous year is essential. Drugs have been shown to precipitate eruptions resembling pemphigus foliaceus most commonly, but also those resembling pemphigus vulgaris. In some cases, ophthalmic eye drops have been associated [90]. Some drugs precipitate an immune response with antibody formation, which leads to acantholysis by an immune mechanism identical to that of idiopathic pemphigus. Other drugs are postulated to induce acantholysis directly. Drugs causing pemphigus belong to one of three groups: thiols, phenols, and non-thiol/non-phenols [91]. Thiol drugs are the most common cause and include penicillamine and captopril. Thiols may induce acantholysis directly but tend to present with a pemphigus foliaceus pattern without oral lesions [92]. Phenols

include aspirin, rifampin, and levodopa, and may induce acantholysis via cytokine release from keratinocytes. Non-thiol/non-phenols include NSAIDs, enalapril, and calcium-channel blockers, and are more likely to induce acantholysis via an immune mechanism. Patients who develop pemphigus with non-thiols often have risk factors for idiopathic pemphigus, and present with a pemphigus vulgaris pattern with flaccid bullae, erosions, and oral lesions. Morbidity may be significant including pain from lesions, and poor oral intake because of oral lesions. Pemphigus cases due to thiol drugs do appear to be truly drug-induced, and will resolve with drug cessation alone, though sometimes requiring months to fully resolve. Cases due to non-thiols often follow a chronic course identical to idiopathic pemphigus, thus raising the suspicion that some cases are not so much drug-induced as simply unmasked by the drug. In these cases, treatment is similar to that for idiopathic pemphigus, and systemic corticosteroids and/or immunosuppression may be required. Patients with large body surface area involvement may benefit from burn unit care, and are expected to have attendant levels of morbidity and mortality. Mortality in pemphigus is significant, owing to medical complications and infections, and age and comorbidity seem to be adverse prognostic factors [93–97].

3.2.3 Drug-Induced Bullous Pemphigoid

Bullous pemphigoid is a disease of the elderly, but drug-induced causes are relatively uncommon. Two types have been described, drug-induced bullous pemphigoid (DIBP) and drug-triggered [98]. Autoantibodies to recognized bullous pemphigoid antigens are more common in the elderly, although not always associated with disease, and this has been speculated to be because of increased medication use in the elderly [99]. It has been suggested that DIBP occurs in a relatively younger age group, although an exact age range is not specified [100]. Many medications have been associated with DIBP as well as some vaccines [100]. Risk factors for DIBP include dementia, Parkinson's disease, psychiatric disorders, a bedridden state, as well as the use of diuretics and antipsychotics [101–103]. The newer anti-diabetic drug class of dipeptidyl-peptidase-IV inhibitors has also been associated with DIBP in older adults [104–106]. While not specific to DIBP, older age and extent of disease are associated with increased mortality in the elderly with bullous pemphigoid, mainly from complications of sepsis or cardiovascular disease [107, 108]. Several studies have raised the suspicion that high mortality rates in bullous pemphigoid (non-drug induced) may be partly linked to systemic corticosteroid use [108–110]. Drug withdrawal is the essential initial management step in DIBP. If corticosteroids are considered, potent topical corticosteroids appear to be a highly

effective and safer alternative to systemic corticosteroids for bullous pemphigoid [109]. However, some have noted that prolonged or extensive application of topical corticosteroids is a significant risk for skin atrophy in the elderly, and may still have systemic effects [111]. No specific guidelines exist, but low-dose oral corticosteroids in combination with topical agents may be sufficient in DIBP, and corticosteroid-sparing agents are usually not needed [100].

3.2.4 Linear Immunoglobulin A Bullous Dermatitis

Linear immunoglobulin A bullous dermatitis is a rare blistering disorder, which is medication related in some cases (although this has been questioned [112]). Vancomycin is most commonly implicated [112]. It affects young children and older adults. In adulthood, it typically begins after the age of 60 years [113]. It may be difficult to differentiate clinically from bullous pemphigoid. Drug withdrawal is usually sufficient for resolution. Oral and ocular involvement occurs and may lead to significant long-term complications. Drug-induced cases may be more severe, with larger skin erosions, mimicking TEN [114].

3.2.5 Stevens–Johnson Syndrome and Toxic Epidermal Necrolysis

The most severe mucocutaneous blistering reactions are those of the SJS/TEN spectrum. Each of these is characterized by the triad of mucous membrane erosions, target lesions, and epidermal necrosis with skin detachment. Differentiation of these is clinical, based on lesion morphology and the percentage of body surface area involved (SJS <10%, SJS/TEN overlap syndrome 10–30%, >30% TEN). Skin biopsy is essential to rule out mimics (staphylococcal scalded skin syndrome, bullous lupus, pustular psoriasis). In cases of SJS/TEN, target lesions are usually erythematous macules with biphasic targets called 'atypical targets'. These are different from the typical triphasic targets of erythema multiforme major, which is generally not drug-induced and usually occurs in younger adults with herpes simplex virus or *Mycoplasma pneumoniae* infection. Eye involvement is present in up to 40% of survivors and poses a risk for blindness because of corneal scarring [115]. Prognosis can be estimated using the SCORe of Toxic Epidermal Necrolysis (SCORTEN) scoring system, which uses seven variables, one of which is age [116].

The increased vulnerability of elderly patients to downstream complications of illness is highlighted by blistering reactions. In the elderly, mortality increases with increasing body surface area involvement, increasing age, and comorbidity, risk factors that are partly captured in the

SCORTEN score [116–118]. However, the mortality risk persists for up to 1 year after the episode. This trend is analogous to that seen in older patients who experience thermal burns, where age alone but also comorbidity influences outcomes [119–121]. In a large European cohort of older patients with SJS/TEN, 6-week mortality rates were 23% (in-hospital mortality) but mortality rates at 1 year were 34%, indicative of ongoing mortality risk well beyond 6 weeks. This included many patients who were discharged from hospital [117]. Mortality rates at 3 months tended to level off for younger patients or those with fewer comorbidities whereas 25% of older/higher comorbidity patients died between 3 months and 1 year, and this was unrelated to the severity of the initial reaction. Other groups have also found that the presence of multi-morbidity substantially influences prognosis [122].

Management requires hospitalization at a center with expertise in the management of SJS/TEN. Available evidence suggests that intravenous immunoglobulin provides some mortality benefit [115, 123–125]. However, this matter remains to be settled by better-designed trials, and the mean age of patients in most trials is in the 40s or 50s, leaving questions about generalizability in the elderly. Recently, a case report [126], and a case series of ten patients [127] (half of whom were aged over 65 years) have suggested reduced mortality using the tumor necrosis factor- α antagonist etanercept.

3.3 Pustular Reactions

Acute generalized exanthematous pustulosis is a rare but serious pustular eruption. An older term, ‘toxic pustuloderma’, has been used to describe cases of pustular drug eruption, but is now largely subsumed under the umbrella of AGEF. Approximately 90% of cases are drug-induced [128]. AGEF occurs more often in middle-aged patients, but the elderly are also affected [32, 129, 130].

AGEF is characterized by the development of burning/pruritic cutaneous erythema with numerous sterile pustules. This is accompanied by fever, leukocytosis, and sometimes mild eosinophilia. The main differential is pustular psoriasis, though psoriasis usually has a more chronic and gradual course. The rash of AGEF usually occurs without internal organ involvement, but a similar rash may appear in the context of a DRESS reaction. The latency for AGEF is much shorter, usually days, rather than the 2–6 weeks, which is typical of DRESS. The AGEF rash typically begins on the face or in flexural areas, but often generalizes rapidly. Where groups of pustules coalesce, the skin may slough mimicking a positive Nikolsky sign, which can be misinterpreted as SJS/TEN [131]. Mucous membrane involvement is occasionally seen, but is mild and usually limited to a single site (mostly oral). Mild

lymphadenopathy has been reported, as well as slight reductions in creatinine clearance and/or mild elevations of transaminases but generally internal organ involvement is not expected [128]. However, tertiary referral centres may see a higher rate of systemic involvement, with hepatic involvement being the most common, but renal, bone marrow, and pulmonary involvement also reported, and neutrophilia may correlate with the risk of systemic involvement [130, 132].

Drug discontinuation is usually all that is required, and correct diagnosis will avoid the use of unnecessary medications such as antibiotics (a pustular rash and neutrophilia is easily mistaken for acute infection). Corticosteroids may be used. Resolution generally occurs within 10 days. There is a high risk of recurrence with repeated exposure to the offending drug, and repeat reactions are more severe. Patch testing can confirm causation. Histologic examination of a skin biopsy should be performed to confirm the diagnosis and rule out other causes. Gram staining can help exclude skin infection. The prognosis is typically good, but high fever or superinfection of the skin can lead to life-threatening complications, and mortality can occur, which is usually in the elderly and/or multi-morbid patient [133, 134].

3.4 Purpuric Reactions

3.4.1 Anticoagulant Skin Necrosis

Purpuric lesions are common in the elderly. Senile purpura may be due to skin aging alone, but is often exacerbated by the use of anticoagulants or antiplatelet agents. The key distinguishing feature that should be sought for all purpuric lesions is whether or not they are palpable. Non-palpable senile purpura is generally owing to extravasation of blood into the dermis, and is usually of cosmetic concern but nothing more. With respect to drug-related causes, palpable purpura may be a sign of either anticoagulant skin necrosis, or hypersensitivity vasculitis. Other causes of vasculitis need to be ruled out.

Anticoagulant skin necrosis is seen with warfarin and heparin. Warfarin causes a transient hypercoagulable state owing to more rapid suppression of anticoagulant factors protein C and protein S [135]. Warfarin-induced skin necrosis (WISN) leads to microvascular thrombus formation in cutaneous and subcutaneous venules with hemorrhagic infarction and skin necrosis [136]. This typically begins 3–5 days after initiation of warfarin, especially when high loading doses are used [137–139]. Painful red plaques develop in adipose-rich areas and may blister, ulcerate, or develop into necrotic hemorrhagic areas. Overall WISN is rare, though the exact incidence is not well defined [140–142]. The incidence may increase with

age [143]. The classic description has been of an overweight perimenopausal woman beginning treatment for venous thromboembolism [144]. However, cases in older patients are well described and the female preponderance remains [136, 145–150]. Treatment involves cessation of warfarin, vitamin K, and heparin at therapeutic doses. Fortunately, the novel oral anticoagulants (NOACs) are not associated with skin necrosis by virtue of their alternative mechanisms of action. They have actually been used to treat warfarin skin necrosis in a few cases [151, 152]. WISN can be very severe, requiring extensive surgical debridement, and mortality is a possibility [136, 153–155].

Heparin-induced skin necrosis can also be seen. It appears to affect patients of a similar age range to WISN, also with a female preponderance [156–158]. This most often occurs at sites of subcutaneous or intravenous heparin injection, though distal sites such as fingers and toes can be affected, and limb gangrene can occur [156, 159, 160]. It is often a clinical feature of heparin-induced thrombocytopenia type 2 (HIT2), although can occur in isolation [161, 162]. In HIT2, it is the result of immune-complex formation with platelet activation leading to thrombosis of the skin [163]. HIT2 appears more likely after the use of unfractionated versus low-molecular-weight heparin [164, 165]. In HIT2, age is not a risk factor for thrombotic complications, though high antibody titers, lower platelet counts, and recent orthopedic surgery may be [163]. Hematology consultation may be needed to establish the diagnosis, which is very important because patients must avoid all future heparin exposure. Heparin-induced thrombocytopenia is also a prothrombotic state that benefits from anticoagulation, though warfarin is not acceptable acutely as it may increase the risk of venous thrombosis and warfarin-induced skin necrosis [154, 155, 160]. The only approved treatment currently is argatroban, though the NOACs are increasingly being considered [166, 167]. There is a mortality risk, which is probably higher in the elderly [158].

3.4.2 Drug-Induced Vasculitis

The nomenclature of drug-induced vasculitis is confusing. Other terms often used interchangeably are hypersensitivity vasculitis, leukocytoclastic vasculitis, allergic vasculitis, cutaneous vasculitis, or serum-sickness/serum-sickness-like reaction [168]. In patients with small vessel vasculitis confined to the skin, drugs are probably the most common cause [169, 170], though proving causation is difficult and there are no histopathologic findings that reliably do so [171]. No clear age predilection appears to exist for drug-induced vasculitis.

The typical feature of vasculitis is palpable purpura in the lower extremity or other dependent areas, though any

location can be involved [169, 170]. Urticarial areas may be seen, but as noted previously, vasculitic urticaria usually remains in fixed locations longer than 24 h. Drug-induced vasculitis may also involve internal organs and kidney, liver, bowel, or central nervous system involvement may become life threatening [170–172]. Establishing the diagnosis is difficult because a long list of autoimmune and infectious causes should be ruled out first [173, 174]. Laboratory studies may show positivity for anti-neutrophil cytoplasmic antibodies (ANCA), though drug-induced cases seem more associated with perinuclear ANCA (p-ANCA) [175–177]. Treatment involves drug cessation and symptomatic treatment of lesions. Patients without systemic involvement usually follow a benign course [169, 170]. Systemic corticosteroids and immunosuppression may be required in more severe cases, especially those associated with ANCA positivity [177]. Age is a predictor of complications and mortality in ANCA-vasculitis from other causes [178, 179].

3.5 Other Uncommon Reactions

3.5.1 Drug-Induced Subacute Cutaneous Lupus Erythematosus

Drug-induced systemic lupus erythematosus (SLE) is a well-described syndrome that mimics many of the systemic features of classical SLE, although skin manifestations are relatively infrequent [180]. However, drug-induced subacute cutaneous lupus erythematosus (DISCLE) is a clinically and immunologically distinct drug reaction with predominantly cutaneous manifestations [181]. A female preponderance appears to exist for DISCLE but the age of onset is much older than that of classical SLE, and it is more prevalent in Caucasians. Lowe et al. found a mean age of onset of 58 years, and suggested this may be related to increased medication use with aging [181]. Lesions are generally annular or papular, sometimes discoid, and appear in the distribution of sun-exposed skin.

Drug-induced subacute cutaneous lupus erythematosus was originally described in five cases caused by exposure to hydrochlorothiazide [182]. The skin lesions are indistinguishable from non-drug-induced SCLE and the same autoantibodies are present (anti-Ro/SS-A and anti-La/SS-B) [181]. Many drugs have been purported to cause DISCLE. Commonly associated drugs include diltiazem, verapamil, hydrochlorothiazide, terbinafine, ranitidine, leflunomide, and chemotherapeutic drugs (especially taxanes) [181, 183–187]. Another recent study found associations with terbinafine, tumor necrosis factor- α inhibitors, anti-epileptic drugs, and proton-pump inhibitors [188]. One mechanism suggested to underlie SCLE is the induction of a photosensitive state, a common feature of most associated

drugs. A relatively long incubation time is a feature of DISCLE, with times ranging from 6 months to 5 years for hydrochlorothiazide and the calcium-channel blockers [182, 189, 190], whereas antifungal treatments may be shorter, on the order of weeks [191, 192]. Most cases resolve with withdrawal of the culprit drug.

4 General Discussion

There is a multitude of conditions in the elderly for which appropriate drug therapy carries a risk of a CADR. While the immediate management of drug reactions is important, especially when they are severe, a broader perspective is critical in the care of older patients. The downstream consequences of CADRs are often significant. Baseline multi-morbidity and frailty are often risk factors for poor outcomes including mortality across most of the severe CADRs. In some cases, appropriate therapy for CADRs entails medications that pose a risk for other ADRs (see Table 4).

Consider the cognitively impaired older individual who starts a statin. Perhaps they take extra doses inadvertently, leading to dermatitis and pruritus. A mild drug reaction causing pruritus seems like a nuisance initially, but prolonged scratching leads to superinfection, cellulitis, and hospitalization, complicated by delirium. In a confusional state, a fall results in head trauma and subdural hematoma, prolonged hospitalization, and the potential for permanent cognitive/functional decline, institutionalization, and even mortality.

Co-morbidity and the ‘anticholinergic burden’ must also be considered [38, 193–195]. For example, a patient with underlying Alzheimer’s dementia has reduced baseline activity in the cholinergic system [196]. Perhaps they are on paroxetine for depression, and ranitidine for their gastroesophageal reflux at baseline, both of which have anticholinergic activity. The initiation of the antihistamine diphenhydramine (Table 4) for their pruritus might be tolerable in other situations, but where a pre-existing anticholinergic load is present, diphenhydramine may be the final straw precipitating anticholinergic adverse effects such as confusion, delirium, dizziness, and falls. Chronic use of anticholinergic medications increases the risk for incident dementia [197].

Mortality is the obvious bad outcome in severe drug reactions but there are numerous other significant impacts for those who survive. Even the healthy elderly have reduced physiologic reserve to cope with severe illness. A critically ill patient with a severe drug reaction such as SJS/TEN will be hospitalized in a critical care unit, probably a burn unit, where the incidence of delirium often approaches 80% [198]. They are likely to have fever, pain, sleep

deprivation, prolonged immobility, and exposure to numerous sedatives, corticosteroids, and opioids all of which increase the risk for delirium [45, 199–202]. Episodes of delirium, especially severe or prolonged bouts, increase the risk of permanent cognitive impairment [203]. Mucocutaneous involvement may lead to oral lesions, causing reduced oral intake with nutritional deficiency. Ocular lesions can lead to visual loss. Nutritional deficiency may delay healing of the skin, which is already slower in the elderly [204]. Each day of immobility results in lost muscle mass, which is slow to recover if they are well enough to participate in rehabilitation. Cognitive changes, visual impairment, and deconditioning may increase the risk of falls [205]. Immobility and corticosteroid use cause bone loss, increasing the chance of adverse sequelae such as fractures, should a fall occur. Survivors of SJS/TEN [206] as well as critical illness and delirium [207, 208] may have lasting post-traumatic stress, anxiety, and depression. These changes may all contribute to a state of increasing frailty, and perhaps invite the use of other drugs. It is therefore not surprising that the risks of morbidity and mortality persist for many months or longer after patients experience critical illness owing to a severe CADR.

The proactive involvement of a geriatrician should be considered in select cases, especially those of hospitalized elderly patients who have had a severe drug reaction. This may be beneficial in the identification of previously unidentified problems or risks, proactive minimization of treatment-related adverse outcomes, and better estimation of prognosis and outcomes in the face of competing comorbidities. Identification of cognitive impairment may be important for safe medication use in the future. Qualitative identification of frailty can be easily performed using Rockwood’s Clinical Frailty Scale, which has considerable prognostic significance, and may help guide treatment decisions [22]. Frail older people who receive inpatient comprehensive geriatric assessment are more likely to return home, less likely to experience cognitive or functional decline, and have lower in-hospital mortality [145]. The proactive approach of geriatrics has been shown to reduce delirium and medical complications in other inpatient settings [209–211]. Given that recovery may be prolonged, and downstream risks linger for months after a CADR, periodic reassessment and optimization may be also facilitated by a geriatrician.

5 Conclusions

The elderly are at risk for a variety of CADRs ranging from the annoying to the life threatening. These may be differentiated clinically by their morphological characteristics.

Polypharmacy and medical comorbidity are common in the elderly and increase the risk for CADR. All drug reactions should be taken seriously, managed appropriately, and monitored for resolution because even minor drug-reactions and their subsequent symptoms or treatments may have broad and significant downstream consequences for the older individual. The consequences of CADR may persist long after the initial episode in the elderly. This is often related to the presence of multi-morbidity and geriatric syndromes, which may go unrecognized or underappreciated. Proactive involvement of a geriatrician has proven efficacy in reducing complications in hospitalized elderly people and should be considered in all older individuals with severe drug reactions.

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