



Cutaneous adverse drug reactions in the elderly

Yee Kiat Heng and Yen Loo Lim

Purpose of review

Population ageing is a worldwide phenomenon. The presence of multiple comorbidities, polypharmacy, age-related changes in pharmacokinetics and pharmacodynamics, as well as skin changes in the elderly contribute to a unique diagnostic and management problem. This article reviews the epidemiology of cutaneous adverse drug reactions in the elderly and elaborates on a few specific types of reactions which are more relevant to the elderly.

Recent findings

Chronic dermatoses, for example, eczema, have been reported to be associated with the use of long-term medications such as calcium channel blockers and hydrochlorothiazide. Elderly patients receiving treatment for cancers may develop chemotherapy-related cutaneous side effects, including those associated with newer 'targeted' molecular therapies. Elderly patients who develop severe cutaneous adverse drug reactions, such as Stevens–Johnson syndrome and toxic epidermal necrolysis, have worse prognosis in terms of mortality.

Summary

Persons of advanced age often have multiple comorbidities and are on multiple medications. This can result in higher probability of an elderly person developing drug eruptions. It is important for the clinician to be aware of the range of drug-related eruptions and their implications.

Keywords

drug eruption, elderly, polypharmacy, toxic epidermal necrolysis

INTRODUCTION

Population ageing is a worldwide phenomenon which has implications for medical care. The WHO defines 'elderly' individuals as being over the age of 65 years in developed countries or 60 years in developing countries [1]. The United Nations predicts that the elderly population (aged 60 years or above) globally will more than double, from 841 million in 2013 to more than 2 billion in 2050, and that the elderly are expected to make up a larger proportion of the world population, increasing from 11.7% in 2013 to 21.1% in 2050 [2]. Furthermore, the segment of persons aged 80 years and above is likely to increase from 14% in 2013 to 19% of the aged population in 2050 [2].

With increasing age, the prevalence of multiple comorbidities rises, with hypertension, hyperlipidaemia, diabetes mellitus, cardiovascular diseases, cancer, joint arthrosis and mental disorders among the most common [3]. As a result, the concurrent use of multiple medications, or polypharmacy, is common in older persons [4]. The elderly population is also reported to be more likely to self-medicate with

non-prescription drugs including homeopathic medications [5].

Adverse drug reactions are a problem in all populations, contributing to hospital admissions and diagnostic and management difficulties in hospitalized patients [6]. Polypharmacy, age-related changes in pharmacokinetics and pharmacodynamics, and more frequent drug–drug interactions [7] potentially contribute to an increased risk of developing adverse drug reactions in the elderly.

Although cutaneous adverse drug reactions (CADRs) may be more common in the elderly, there are relatively few recent articles in the literature which specifically address this problem [8,9,10, 11–13]. We discuss the current literature with regard to the epidemiology of CADR, cutaneous reaction

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KEY POINTS

- Ageing-related skin changes and concurrent use of multiple medications make the diagnosis of drug eruptions more challenging in the elderly.
- Cutaneous eruptions associated with new targeted chemotherapy drugs have been identified.
- Associations between chronic dermatoses and long-term medication use have been reported.

patterns associated with drugs commonly used in the elderly, drug eruptions which have worse prognosis due to advanced age and/or comorbidities, and the challenges of managing drug eruptions in the elderly.

EPIDEMIOLOGY

The epidemiology of cutaneous drug hypersensitivity reactions has been comprehensively reviewed in the past few years [14,15], but there are relatively few data specific to the elderly. Current available information is derived from studies of heterogeneous design, and may possibly be imprecise as causality of the reported reactions is not stated or established in most studies.

It has been shown in one study [11] that about 8% of all adverse drug reactions diagnosed in older persons in an ambulatory setting was 'dermatologic/allergic' in nature. In another study [16] from Brazil, non-serious 'skin rash' contributed to about 8% of all adverse drug reactions diagnosed in a cohort of elderly hospitalized patients. Looking specifically at CADRs, its prevalence, regardless of age, is reported to range from 0.4 to 2.2% in hospitalized patients [17–19]. Studies from Malaysia [20] and China [21] showed that 17.5 and 21.4%, respectively, of CADRs among hospitalized patients occurred in the elderly.

It is well reported that maculopapular exanthema and urticaria are the most common CADRs, whereas Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) and drug rash with eosinophilia and systemic symptoms (DRESS) are infrequent or rare in the overall population [18,19,22–24]. There are a few studies [10^a,17,21,25,26] focusing on older or elderly patients, and these suggest that the prevalence of CADRs in the elderly is generally not different from that in the overall population. However, it has been reported in one study [27] that severe reactions such as SJS/TEN, DRESS and anaphylaxis are more common in non-elderly patients.

Previous reviews [8,9] have discussed the clinical features and drugs commonly involved in CADRs in the elderly. In the following sections, we focus on

selected reactions in the elderly which may pose diagnostic or management difficulties.

Chronic eczematous eruptions and cardiovascular medications

In the elderly, xerosis and eczema are the commonest skin disorders [28], whereas hypertension is the commonest medical comorbidity [3]. The possible association between eczema and hypertension medication was first reported by Morin *et al.* [29] in 2002. In their retrospective series of 89 elderly patients with recurrent or chronic extensive eczema, almost half had no identifiable cause. These patients were more likely to have chronic drug use, including calcium channel blockers (CCBs), diuretics, angiotensin-converting enzyme (ACE) inhibitors and nitrates.

Joly *et al.* [12] subsequently showed, in a multi-centre case-control study in 2007, that chronic use of CCBs was significantly associated with chronic eczematous eruptions in the elderly, with an adjusted odds ratio (OR) of 2.5 [95% confidence interval (CI) 1.3–4.6]. To determine causal association, the authors performed two further ancillary studies which showed that most of the patients had resolution of the rash upon withdrawal of the CCB after an average of 3 weeks. Most patients who were later re-challenged to the CCBs had the eruption reproduced within a mean of 3.8 ± 1.9 days. Summers *et al.* [13] in 2013 provided further evidence to support the association of eczema in the elderly, who were on CCBs, and in addition, the association with the use of thiazides. In this retrospective case-control study involving 94 cases and 132 age, sex and race-matched controls, the authors showed significant association of CCBs (matched ORs 4.21, 95% CI 1.77–9.97) and thiazides (matched OR 2.07, 95% CI 1.08–3.96) with eczema. The pathogenesis of drug-related eczema is poorly understood. On a cellular level, calcium homeostasis plays an important role in maintaining healthy skin function. Very low calcium concentrations are required at the stratum basale to allow self-renewal and division of the keratinocyte stem cells, whereas high calcium concentrations are needed higher up in the epidermis for keratinocyte differentiation and skin barrier formation [30]. It was recently shown that this epidermal calcium gradient is lost in the process of skin ageing [31]. It may be postulated that the use of CCBs in elderly further disturbs calcium homeostasis, resulting in impaired skin barrier function. Similarly, sodium channels in the skin are recognized to have a role in epidermal differentiation [32], and the use of hydrochlorothiazide, which blocks sodium–chloride co-transporter, may affect skin barrier function.

Apart from CCBs and thiazides, ACE inhibitors and angiotensin II receptor blockers have also been implicated in drug-induced eczema. Vena *et al.* [33] reported a series of 23 elderly patients with eczema related to the use of these drugs. Eczema resolved in all cases after drug withdrawal and recurred in 7 out of 11 patients with re-introduction of the drug, within an average of 3–4 months. Cholesterol-lowering medications, particularly the statins, can also cause skin dryness and eczematous reactions by disruption of the skin barrier due to their effects on cholesterol biosynthesis [34]. However, larger case-control studies are needed to confirm the associations of cutaneous eruption with these other drugs.

In clinical practice, patients with drug-related eczematous eruptions may be easily dismissed as having endogenous eczema when no apparent cause is found. It can be difficult to relate the eczematous rash to these drugs due to the long latency period, as well as the insidious onset of the eczema. The latency period was reported by Joly *et al.* [12] as a median of 3 months for CCB-associated eczema. Figure 1 shows an example of a patient with extensive eczema related to amlodipine. It is currently unknown if skin tests such as drug patch tests are useful in the diagnosis of such eruptions. However, if the reaction is due to the drug's mechanism of action and not 'allergic' in nature, skin patch tests

are unlikely to be useful. Until further studies are available, it may be prudent to consider drug withdrawal, especially of CCBs or thiazides in elderly patients, in whom eczema fails to respond to adequate topical therapy.

Psoriasis and beta-blockers

The onset of psoriasis has a bimodal age distribution. The mean age of late-onset psoriasis ranges from 55 to 60 years – an age range in which comorbidities such as hypertension and hence the use of anti-hypertensive patients is also common. There have been conflicting studies [35,36] about the association of psoriasis with the use of beta-blockers. In a recent large prospective cohort study [37] of 77 728 women with hypertension, of whom 834 developed psoriasis during the 10 663 39 patient-years of follow-up, it seemed that long-term regular use of beta-blockers increased the risk of psoriasis. It is postulated that blocking of beta-adrenergic receptors in the skin leads to a decrease in cellular levels of cyclic adenosine monophosphate, resulting in increased cell growth and reduced cellular differentiation. While association does not mean causality, there may be a role of cessation of beta-blockers in elderly patients who have recalcitrant psoriasis if the potential benefits outweigh the risks.

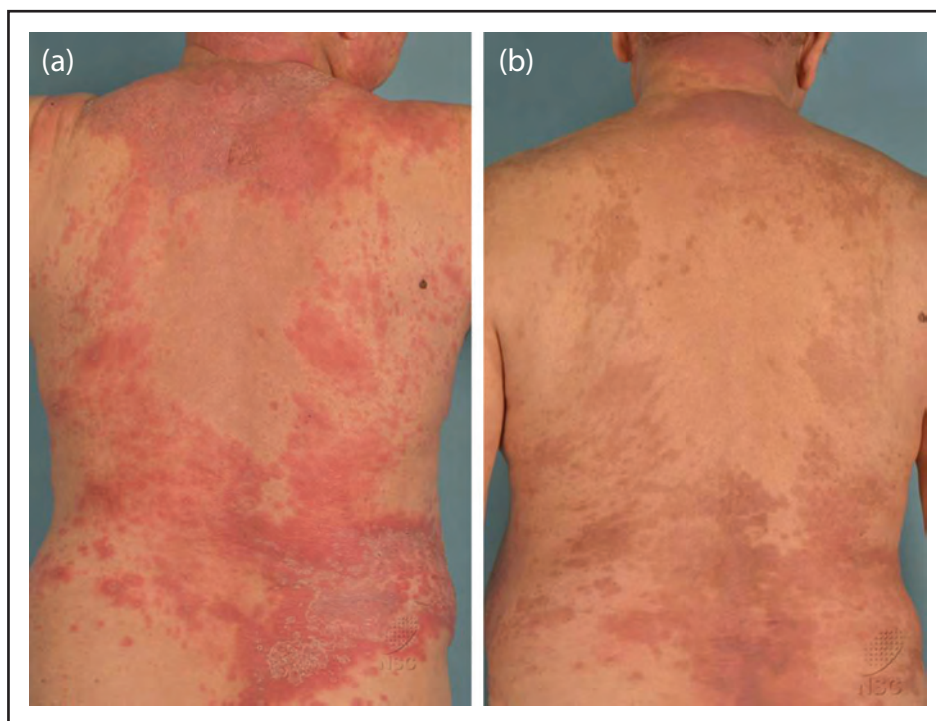


FIGURE 1. (a) Chronic extensive eczematous eruption of insidious onset in an elderly man. Amlodipine was started 4 weeks before onset of the rash. (b) The rash promptly resolved after stopping amlodipine, with residual post-inflammatory hyperpigmentation. Re-exposure to amlodipine resulted in recurrence of the rash within 2 weeks.

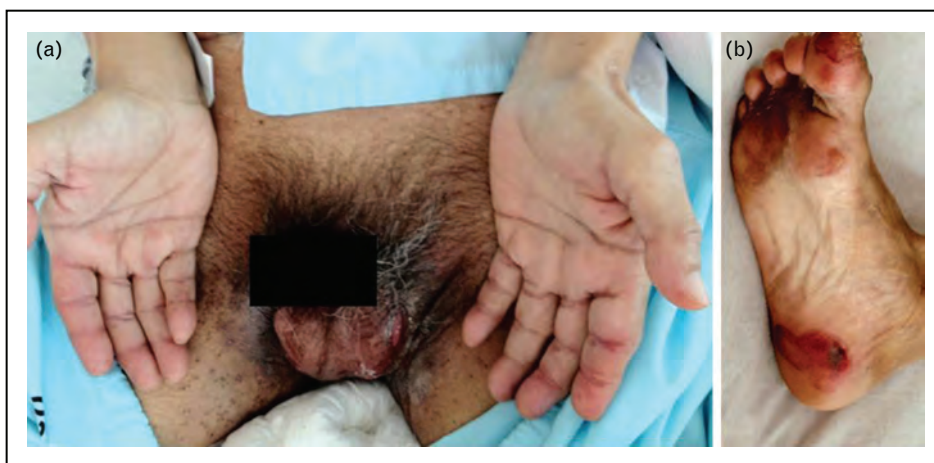


FIGURE 2. (a) Toxic erythema of chemotherapy presenting as erythematous patches with erosions at the intertriginous areas and erythema of the palms. (b) The same patient had painful erythematous patches with blistering and erosions on the sole of the right foot. Similar lesions were present on the left foot.

Chemotherapy-related cutaneous reactions

Ageing is a risk factor for cancer, of which lung, colorectal, breast, prostate and stomach cancers are among the most common [38]. When complete cure is not possible, significant advances in oncological care have resulted in many cancers being controlled and managed for long periods. Oncology therapies have advanced rapidly in the past decade, with new drugs producing a new range of cutaneous side effects.

Conventional chemotherapeutic agents remain the mainstay of cancer treatment and are recognized to cause alopecia, hyper-pigmentation, paronychia, nail changes and mucositis [39[¶]]. The term toxic erythema of chemotherapy (TEC) was introduced in 2008 as an easily understood clinical term for a range of previously described cutaneous reactions, such as neutrophilic eccrine hidradenitis, araC (cytarabine) ears, hand–foot syndrome (HFS) and acral erythema, which have clinically and histologically overlapping features [40]. TEC presents with erythematous patches and plaques with oedema affecting the intertriginous areas, hands and feet, elbows and knees, with occasional blistering and erosions (Fig. 2). Pruritus, paraesthesia or pain is common. In TEC, the skin manifestations are related to the toxic effects of the chemotherapeutic drugs to the skin or other organs rather than allergic in nature. It is important to recognize them as they can be misdiagnosed as SJS/TEN, symmetrical drug-related intertriginous and flexural exanthema (SDRIFE), graft-versus-host disease, intertigo or contact dermatitis.

Similarly, non-allergic eruptions can also occur in patients receiving the new molecular-targeted treatment agents. These side effects considerably impact patients' quality of life and psychological

well being [41]. The eruption of papules and pustules, in the absence of comedones, predominantly on the face, neck, upper trunk and proximal upper limbs (see Fig. 3), has been frequently associated with drugs targeting the epidermal growth factor receptor (EGFR), for example, erlotinib and cetuximab [42[¶]]. Although disturbing, the presence and severity of papulopustular eruption have been shown to correlate with better tumour response to anti-EGFR agents and survival [43]. The multi-kinase inhibitors (MKIs), for example, sunitinib and sorafenib, may also cause papulopustular eruptions, but more disturbingly may cause hand–foot skin reaction (HFSR) in 10–63% of patients who receive the medication [44]. HFSR is characterized by symmetrical hyper-keratotic plaques, with occasional blistering, on the hands and feet localized to areas of pressure. Pain and debilitation may occur resulting in reduction or interruption of cancer treatment. Prophylaxis, early recognition and treatment of such reactions are vital to holistic patient management. Skin reactions to chemotherapeutic agents are beyond the scope of this article and have been reviewed elsewhere [39[¶],42[¶]].

Severe cutaneous adverse drug reactions in the elderly

Stevens–Johnson syndrome/toxic epidermal necrolysis and DRESS are uncommon life-threatening CADR which may occur in any age group. The median age of patients in the largest cohort of 379 validated cases in the EuroSCAR study [45] was 50 years [inter-quartile range (IQR) 28–68]. Similar findings of older age of patients, including the elderly, have been reported in several other large studies [46–50]. DRESS also occurs in older

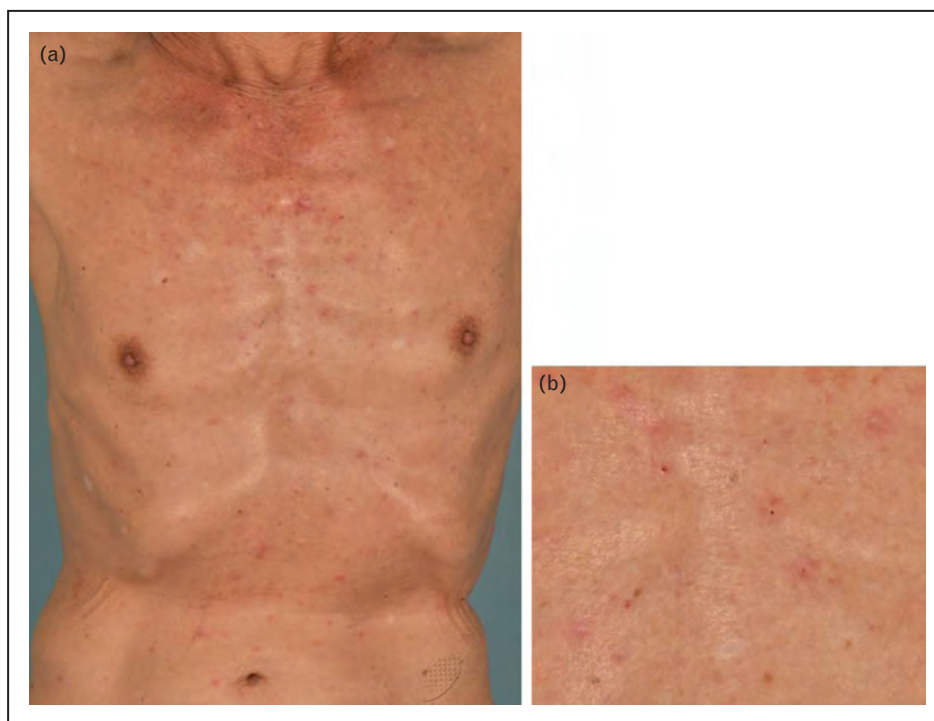


FIGURE 3. (a) An elderly man who was receiving gefitinib for metastatic lung adenocarcinoma developed a pruritic rash predominantly on the face, neck and trunk. (b) On closer examination, the rash consists of papules and pustules without comedones.

individuals, including the elderly, with the median age of involvement reported to be 54.5 and 48 years, respectively, in two large cohorts of patients [51,52].

While SJS/TEN and DRESS do not exclusively occur in the elderly, many drugs, such as allopurinol, oxicam NSAIDs, anti-infective sulphonamides, phenytoin and carbamazepine, which are notorious for causing these CADR, may be used in this population as conditions such as gout, joint pains, infections, cerebrovascular accidents and mood disorders become more common. Strontium ranelate – an anti-osteoporosis drug – deserves special mention as being a chemical element similar to calcium, it was initially considered to be a well tolerated drug. However, since 2009, SJS/TEN has been reported in three elderly Asian women treated with strontium ranelate for postmenopausal osteoporosis [53–55]. In addition, 47 DRESS cases (11 considered ‘established’, 14 ‘probable’ and 22 ‘possible’), with 4 resultant deaths, have been reported [56]. Other osteoporosis drugs are often considered well tolerated, but bisphosphonates have also been reported to cause SJS/TEN in post-marketing surveillance [57].

Age (above 40 years) is one of the prognostic factors included in a composite score (SCORTEN), which is validated to be predictive of mortality in

SJS/TEN [46]. Schneck *et al.* [47] analysed a large cohort of SJS/TEN patients in the multinational EuroSCAR study performed between April 1997 and December 2001. Of the 281 patients analysed, it was reported that those above 70 years old had an increased risk of mortality compared with those less than 40 years old, with univariate OR of 5.7 [95% confidence interval (CI) 2.6–12.5] and multivariate OR of 9.4 (95% CI 4.0–22.5) after adjusting for treatment, disease severity and country. Similarly, in a Taiwanese study [58^{*}] of 37 cases of SJS/TEN caused by antibiotics, the surviving cohort (mean age 48.7 years) was significantly younger than the deceased cohort (mean age 66.5 years), though the SCORTEN was not significantly different.

It is also recognized that there remains a higher risk of mortality for older patients even after recovery from the acute event. Sekula *et al.* reported, on the basis of data collected in the RegiSCAR study [43], that the mortality rate was 23% (95% CI 19–27%) at 6 weeks and 34% (95% CI 30–39%) at 1 year. Severity of the reaction was a risk factor for mortality only in the first 90 days after the onset, whereas serious comorbidities (severe liver or kidney disorders and recent malignancy) and age influenced mortality beyond 90 days and up to 1 year after onset of reaction.

It is important to recognize and manage the long-term sequelae of SJS/TEN as these may adversely impact the quality of life of surviving patients, especially the frail elderly. Dry eyes, corneal scarring with resultant visual impairment, dyspigmentation and mucosal scarring resulting in dental and genito-urinary disorders are known complications of SJS/TEN [59]. In our experience, post-traumatic stress disorder and depression are also not uncommon. Respiratory sequelae are now gaining recognition. Duong *et al.* [60] performed pulmonary function tests in SJS/TEN patients at a median of 3 months after the acute event and reported that whereas none of the patients had respiratory symptoms, more than half of them had abnormalities in alveolar diffusion. This study was performed in a relatively young group of patients (median age 36.5 years) and it remains unknown if such respiratory sequelae also occur in older patients. These pulmonary abnormalities could have an impact on the elderly who already have reduced cardiorespiratory reserves. Improving support to SJS/TEN survivors and improving understanding of mechanisms resulting in long-term sequelae remain priorities for future research and patient care [61].

Advanced age *per se* has not been recognized to be predictive of mortality in DRESS [62–64], but elderly patients with reduced organ reserves may be more vulnerable to end-organ failure [65] with resultant acute mortality and long-term sequelae. Long-term use of systemic corticosteroids, which is the mainstay of treatment for DRESS with severe organ involvement, is also associated with complications such as infections, cardiovascular diseases, osteoporosis, cataract or glaucoma, which are already diseases common in the elderly. Indications for the use of systemic steroids must be strong and close monitoring for complications is recommended.

Challenges in the management of drug eruptions in the elderly

The evaluation of an elderly patient with suspected CADR has unique challenges. Obtaining an accurate history, especially a comprehensive drug history, may be more difficult due to polypharmacy, higher likelihood of self-medication, impaired cognitive function or illiteracy. Morphological diagnosis of the rash is complicated by age-related skin changes such as xerosis, skin atrophy and fragility. Management of CADR usually involves prompt withdrawal of the culprit drug, but this may not be easily identifiable, especially when multiple drugs may be prescribed within the same time frame and consistent with causality. In patients with maculopapular

exanthema, it is prudent to stop the drugs with high risk-to-benefit ratios. Strongly indicated drugs with no suitable replacements may be continued if the reaction is not severe, with close monitoring of the patient's condition for signs of severe reactions such as centropacial oedema, stomatitis, painful skin, purpuric skin lesions, atypical targetoid lesions, blisters, positive Nikolsky's sign, fever and internal organ involvement. Specific treatment of CADRs should be directed to the type of reaction and its severity. In an elderly patient, treatments such as systemic corticosteroids or other immunosuppressants may be poorly tolerated and should be used only if strongly indicated. In particular, intravenous immunoglobulin (IVIg) should no longer be used to treat SJS/TEN as it has potential adverse effects, including acute renal failure [66], and has been shown to be an ineffective treatment modality [48,67,68].

To identify the culprit drug, further evaluation such as skin tests, for example, skin prick, intradermal or patch tests and drug provocation tests (DPTs), may be performed, usually several weeks after the reaction has resolved. We are not aware of the exact effects of age-related skin changes on the accuracy of drug skin tests. It may be postulated that skin atrophy allows more drug penetration and possibly increases the likelihood of irritant patch test reactions, but immune senescence in elderly may also result in lower sensitivity in patch tests. In a study [69] of elderly patients with suspected contact dermatitis, it has been suggested that there may be an age-related decline in positive patch test reactions compared with younger controls and that development of an allergic response may be delayed. The relevance of the findings of this study to drug skin testing is unknown.

Drug provocation tests are the 'gold standard' for establishing causality of CADR or ascertaining tolerability of a tested drug. However, according to the European Network on Drug Allergy (ENDA) guidelines [70], DPTs are relatively contra-indicated in patients with comorbidities such as cardiac, renal and liver problems, in whom positive drug provocation of a potentially severe reaction may result in situations beyond medical control. These medical conditions may preclude the use of DPT in some elderly patients. Nevertheless, DPT can be performed when benefit outweighs the risk in selected patients, for example, eczema related to CCB. Failure to identify the culprit drug may result in future unnecessary avoidance of suspected drugs, leading to the use of alternatives which may have higher cost, less effectiveness and more side effects. It has been reported that clinical history suggestive of NSAID intolerance in younger patients (<40 years

old) is a risk factor for positive DPT to the suspected drug [71], but larger studies are needed to support these findings.

CONCLUSION

Cutaneous adverse drug reactions in the elderly are a problem which is likely to worsen with population ageing and polypharmacy. Whereas new drugs may be more efficacious or 'targeted', they may still cause previously recognized or novel types of drug eruptions. Post-marketing pharmaco-surveillance is important to identify reaction patterns which may be associated with newly introduced drugs as shown in the example of strontium ranelate. The relationship between chronic dermatoses and drugs needs to be further investigated with well designed epidemiological studies. Future studies should aim to evaluate the impact of drug eruptions in the elderly on quality of life issues, overall disease management, as well as the impact of ageing on the process of drug hypersensitivity evaluation. Finally, further efforts must be made to educate physicians in order to reduce unnecessary prescriptions and polypharmacy in the elderly.

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Conflicts of interest

There are no conflicts of interest.

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- of outstanding interest

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