International Journal of Dermatology

Review

Update on the use of dapsone in dermatology

Nohra Ghaoui[1], MD, Edith Hanna[2], MD, Ossama Abbas[3], MD, Abdul-Ghani Kibbi[3], MD and Mazen Kurban[3,4], MD

[1]Department of Internal Medicine, American University of Beirut, Beirut, Lebanon, [2]Department of Dermatology, University of Toronto, Toronto, ON, Canada, [3]Department of Dermatology, American University of Beirut, Beirut, Lebanon, and [4]Department of Biochemistry and Molecular Genetics, American University of Beirut, Beirut, Lebanon

Correspondence
Mazen Kurban, MD
Department of Dermatology
Biochemistry and Molecular Genetics
American University of Beirut Medical Center
Riad El Solh
P.O. Box 11-0236
Beirut 1107 2020
Lebanon
E-mail: mk104@aub.edu.lb

Conflict of interest: None.
Funding source: None.

doi: 10.1111/ijd.14761

Abstract

Dapsone (4,4'-diaminodiphenylsulfone) is the only remaining sulfone used in anthropoid therapeutics and is commercially available as an oral formulation, an inhaled preparation, and a 5% or 7.5% cream. Dapsone has antimicrobial effects stemming from its sulfonamide-like ability to inhibit the synthesis of dihydrofolic acid. It also has anti-inflammatory properties such as inhibiting the production of reactive oxygen species, reducing the effect of eosinophil peroxidase on mast cells and down-regulating neutrophil-mediated inflammatory responses. This allows for its use in the treatment of a wide variety of inflammatory and infectious skin conditions. Currently in dermatology, the US Food and Drug Administration (FDA)-approved indications for dapsone are leprosy, dermatitis herpetiformis, and acne vulgaris. However, it proved itself as an adjunctive therapeutic agent to many other skin disorders. In this review, we discuss existing evidence on the mechanisms of action of dapsone, its FDA-approved indications, off-label uses, and side effects.

Introduction

Sulfones are old antimicrobial and chemotherapeutic agents which were used to treat infections caused by streptococcus, mycobacteriaceae, and other bacteria.[1] Nowadays, dapsone (4,4'-diaminodiphenylsulfone) is the only remaining sulfone used in anthropoid therapeutics.[2]

The year 1908 marks the discovery of dapsone by Professor Emil Fromm, a German professor of organic chemistry along with his colleague, Jakob Wittman.[3] Dapsone was conceived as a therapeutic agent in 1937 upon the discovery of its anti-inflammatory properties in infected mice.[4–6] In 1950, Esteves and Brandão reported an incidental successful use of dapsone in treating dermatitis herpetiformis.[7] Furthermore, the success of dapsone was reported in subcorneal pustulosis, which resulted in complete remission of the disease.[8]

Dapsone is commercially available as a topical (5% and 7.5% gel), oral, and inhaled formulation. The dual antimicrobial and immunomodulatory effects of dapsone were pivotal in preventing and treating leprosy and *Pneumocystis jiroveci* among HIV patients, as well as in chronic inflammatory diseases. Moreover, dapsone was effective in treating autoimmune bullous eruptions and in managing neutrophil-mediated processes.[9]

The most recent review of the clinical uses of dapsone conducted by Wozel and Blasum in 2014 failed to include a vast majority of dermatologic diseases because of lack of experience with this drug in the past.[2] We hereby present a comprehensive overview in which we review dapsone's mechanisms of action and its FDA-approved clinical indications in treating dermatologic entities. More importantly, this review offers a special emphasis on the off-label uses of dapsone in dermatology to showcase that this drug, once thought to be an ancient drug, has extended its uses to newer indications in which it was highly effective; thus physicians should strongly reconsider dapsone as a solid adjuvant therapeutic agent to many dermatologic entities, detailed in this paper.

Mechanism of action

Dapsone carries both bacteriostatic and anti-inflammatory properties. Its antimicrobial effect stems from its sulfonamide-like

ability to inhibit the synthesis of dihydrofolic acid.[10] Additionally, dapsone has multiple anti-inflammatory properties. It inhibits the production of reactive oxygen species directly and reversibly inhibits the myeloperoxidase enzyme thus decreasing hypochlorous acid formation.[11] Dapsone inhibits beta-2 integrin (CD11b/CD18)-mediated adherence of neutrophils[12] and down-regulates interleukin 8 (IL-8), which plays a primordial role in neutrophil-mediated inflammation, as well as regulates the functions of lymphocytes and monocytes.[13]

Along with its ability to interfere with the function of other proteins in the integrin family (leukocyte-function-antigen, Mac-1, p150,95), dapsone has an inhibitory effect on prostaglandin synthesis and liberation, in a dose-dependent manner (Fig. 1). Similarly, dapsone has been found to cause a dose-dependent inhibition of TNF-α and the generation of leukotriene products in polymorphonuclear leukocytes.[14]

In regards to the effect on neutrophils, dapsone has a potent activity in reducing the effect of eosinophil peroxidase on mast cells, which results in a decreased liberation of histamine.[15] Finally, dapsone was shown to inhibit the alternative pathway of complement activation in vitro, but such property was not reproduced in vivo.[16]

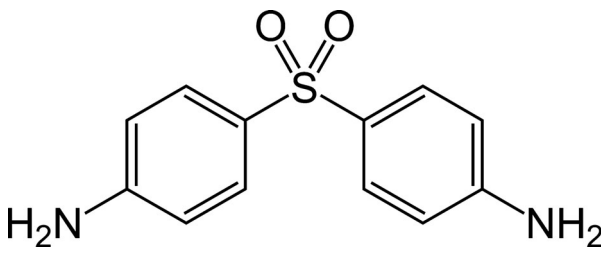

Figure 1 Dapsone's molecular formula of $C_{12}H_{12}N_2O_2S$

FDA-approved indications for dapsone use in cutaneous disorders

In dermatology, the FDA-approved indications for dapsone are leprosy, dermatitis herpetiformis,[17] and acne vulgaris.[18]

Leprosy

Similar to tuberculosis, the treatment of leprosy consists of multidrug therapy, including dapsone, rifampin, and clofazimine. Monotherapy is associated with higher risk of resistance.[19] Two regimens were issued by the WHO according to the type of infection: paucibacillary leprosy (less than five lesions, no bacteria detected) and multibacillary leprosy (more than five lesions, bacteria detected). Both regimens contain dapsone.

Dermatitis herpetiformis

Dapsone is the only FDA-approved drug for treating dermatitis herpetiformis during the 6- to 24-month period until the gluten-free diet is effective.[20] It is prescribed at a starting dose of 50 mg/day in order to minimize potential side effects and gradually increased up to 200 mg/day until the disease is controlled.[21] A dose of 0.5–1 mg/kg/day is used in the maintenance phase to control the itching and prevent the development of new skin lesions.[22]

Acne vulgaris

Since its FDA approval in 2008, topical dapsone 5% gel has been approved for the use in many clinical indications, including acne vulgaris. Dapsone is highly effective in the treatment of adult female acne when compared with adolescent females.[23] Topical dapsone 5% twice daily was reported to be efficacious and safe, yet few cases of G6PD methemoglobinemia were found, and the FDA decided to change the label in July 2015 to "caution of use." In such cases, patients should seek help if buccal mucous membranes, lips, or nail beds become cyanotic. Additionally, topical application followed by benzoyl peroxide could lead to temporary local yellow-orange discoloration of the skin as well as facial hair which would resolve within days to months.[24]

After several years of topical dapsone use, researchers started investigating the emergence of potential microbial resistance and skin microbiome alterations. In 2015, Sardana *et al*. found that dapsone was an ideal agent to treat acne and to prevent resistance against *Propionibacterium acnes*.[25] A year later, Zhanel *et al*. found that local skin concentrations of dapsone after topical application are above concentrations needed to inhibit microbial growth of pathogenic or potentially pathogenic organisms.[26] Levels of dapsone were found high enough to inhibit gram-positive cocci like *Staphylococcus* spp. and *Streptococcus* spp. which may eventually result in resistance to dapsone or to other antimicrobials. Further studies should be conducted to verify this claim.

In 2017, the FDA approved the use of topical dapsone 7.5% gel for acne vulgaris. Its advantage is that it ameliorates patients' compliance and convenience (≥12 years old) as it is found efficient with once daily application instead of twice daily like with dapsone 5% gel.[27] Reduced acne severity and reduced inflammatory and noninflammatory lesion counts were noted with daily use of dapsone gel 7.5%, starting 2 weeks after treatment and onward.[28]

Furthermore, systemic dapsone could be an effective and safe alternative to isotretinoin in severe acne vulgaris recalcitrant to other topical or systemic drugs. Several case reports found that oral dapsone could be an excellent alternative drug when treating severe acne (nodulocystic or conglobata acne) unresponsive to topical benzoyl peroxide, topical adapalene, oral tetracycline, oral isotretinoin, and oral methylprednisolone.[29,30]

Off-Label uses of dapsone in cutaneous disorders

Dapsone has been used as an off-label drug for a multitude of dermatologic entities given its anti-infectious and antiphlogistic characteristics. It has shown efficacy as prophylaxis for infectious diseases and in treating multiple inflammatory diseases

including but not limited to neutrophilic and eosinophilic diseases, bullous disorders, granulomatous inflammation, and vasculitis. Cutaneous lupus erythematosus, prurigo pigmentosa, relapsing polychondritis, and rheumatoid arthritis have also been reported to respond to dapsone.[2,9]

Infectious diseases

Toxoplasmosis

Dapsone is a valid therapeutic choice for both treatment and prophylaxis of ocular, pulmonary, or neurologic toxoplasmosis. Oral dapsone 100 mg daily is efficient for the treatment of infection by *Toxoplasma gondii*, whereas oral dapsone 50 mg daily would be sufficient for prophylaxis. Dapsone 50 mg daily with pyrimethamine 50 mg along with folinic acid 25 mg weekly is another alternative for toxoplasmosis prophylaxis.[31]

Plasmodium falciparum

In the absence of sulfa allergy, G6PD deficiency, and anemia (hemoglobin <7), the WHO considers chlorproguanil-dapsone an efficient treatment modality of uncomplicated *Plasmodium falciparum*.[32] However, this double therapy was withdrawn from the market, post-licensure, in 2008 because of hemolytic toxicity in patients, especially those with G6PD deficiency.[33] However, an interesting study conducted by Enwere and Falade[34] discovered that despite the higher risk of intravascular hemolysis with chlorproguanil-dapsone compared to sulfadoxine-pyrimethamine (another chemoprophylactic regimen for malaria), the risk of hemolysis in G6PD-deficient patients is increased with either drug, and no study shows superiority of any of those combination therapies.

Inflammatory diseases

Acne inversa

Acne inversa, or hidradenitis suppurativa (HS), is defined by perifollicular inflammation resulting in fibrosis of the affected area. Treatments required are classified as anti-inflammatory and antibacterial drugs. Cases of mild to moderate hidradenitis are effectively treated with antibacterial drugs. However, as they progress to severe inflammation, anti-inflammatory regimens like TNF-α inhibitors are required to control the inflammation.[35]

A review of treatments for HS in 2017[35] suggested that dapsone, given its anti-IL8 and anti-TNF-α immunomodulatory characteristics,[36] is an effective therapeutic agent in the treatment of HS.

In 2006, Kaur and Lewis[37] treated five cases of refractory HS with 50–150 mg of dapsone daily, and all patients showed improvement after a mean of 8 weeks. In 2011, Yazdanyar *et al*.[38] treated 24 patients with 50–200 mg of dapsone daily with nine patients showing clinically significant improvements. In 2015, Staub *et al*.[39] described successful treatment of PASH (pyoderma gangrenosum, acne, suppurative hidradenitis) syndrome of a 22-year-old woman who failed remission with a combination of etanercept, adalimumab, fumaric acid, and anakinra (IL-1 receptor antagonist). Upon switching to IV infliximab, cyclosporine, and dapsone, the patient noted clinically significant improvement. In 2017, Khandalavala[40] reported a disease-modifying approach for advanced HS using metformin, liraglutide, dapsone, and finasteride. This regimen resulted in a clinical remission of her disease with resolution of her obesity and associated hypoalbuminemia.

Finally, adding dapsone 100 mg daily to isotretinoin 80 mg daily results in significant clearing of dissecting cellulitis (perifolliculitis capitis abscedens et suffodiens) when isotretinoin alone is not enough.[41]

Rosacea

Rosacea is a common inflammatory skin disorder. Combining topical treatments with oral antibiotics (minocycline, doxycycline, erythromycin, etc.) is usually necessary to treat papulopustular variants of rosacea. Additionally, dapsone 7.5% gel can also be used once daily for up to 12 weeks.[42] Systemic administration of dapsone has also shown success in treating granulomatous rosacea and rosacea fulminans.[43]

Granuloma annulare

Granuloma annulare (GA) is a benign granulomatous inflammation of the dermis. Kassardjian *et al*. reported significant clinical improvement of a periocular GA with dapsone 5% gel twice daily for 3 weeks, proving the usefulness of this modality for the treatment of cosmetically sensitive areas.[44] Lukacs *et al*. conducted a systematic review that concluded the administration of systemic dapsone 100 mg or 200 mg should be considered as first-line treatment, when steroids and calcineurin inhibitors fail, with expected clearance of all lesions in up to 3 months.[45]

Lupus miliaris disseminatus faciei

Lupus miliaris disseminatus faciei (LMDF) is a rare disease characterized by chronic inflammatory benign dermatosis of unknown etiology exemplified by red-brown papules on the forehead, cheeks, and eyelids. El Benaye *et al*. reported two patients with LMDF who were treated with dapsone 100 mg daily.[46] No new lesions developed after treatment initiation with reduction in disease evolution period. The patients remained in remission during the 8-month time lapse of the study follow-up. Sardana *et al*.[47] reviewed major reports of treatments and their response in LMDF and concluded that antibiotics, especially dapsone, are mostly effective in the early inflammatory stage of the disease. In the granulomatous stages, however, clofazimine would be more efficient.

Familial mediterranean fever

Familial mediterranean fever (FMF) is a hereditary autoinflammatory disease that presents with recurrent febrile attacks and polyserositis. The paroxysmal attacks of FMF are because of

neutrophil activation at the serosal surfaces.[48] Colchicine is the gold standard in preventing these acute attacks because of its inhibitory effect on chemotaxis and phagocytosis of neutrophils in serosal surfaces. However, around 5–10% of patients are resistant to colchicine.

Salehzadeh *et al*. conducted a study in children with FMF to evaluate efficacy of dapsone in colchicine resistant patients.[49] Dapsone 2 mg/kg administered in single dose daily for an average of 6 months was found to achieve remission and acute attack control in 50% of patients who were colchicine resistant with no significant side effects. This drug could thus be considered when dealing with colchicine resistant FMF cases.

Neutrophilic diseases

The use of dapsone in treating neutrophilic diseases is already well established given its role in inhibiting beta-2 integrin-mediated adherence of neutrophils and downregulation of IL-8.[12] Two neutrophilic dermatoses responding to a combination regimen containing dapsone are Sweet's syndrome, also known as febrile neutrophilic dermatosis, along with recurrent neutrophilic dermatosis of the dorsal hands.[2,9] Additionally, Bhat *et al*.[50] and Pereira *et al*.[51] conducted studies that led to partial-to-complete remission in patients with pyoderma gangrenosum (PG) treated with systemic corticosteroids in combination with other therapies, including dapsone and other systemic immunosuppressants (cyclosporin, cyclophosphamide, etc.). The efficacy of dapsone in PG has been attributed to its effect on matrix metalloproteinases, T cells, and cytokines.[52] In a recent retrospective review, 27 patients with PG from Massachusetts General Hospital and Brigham and Women's Hospital were treated with systemic dapsone for 4 weeks.[53] On follow-up, 15.6% reported complete healing along with 81.3% reporting partial improvement. This further corroborates that dapsone may be a systemic nonimmunosuppressant adjuvant treatment for this neutrophilic dermatosis.

Eosinophilic diseases

The inhibitory effect of dapsone on eosinophil peroxidase explains the successful use of dapsone in treating eosinophilic diseases. It has long been established that chronic idiopathic urticaria or delayed pressure urticaria (IgE), eosinophilic fasciitis, and eosinophilic folliculitis (Ofuji's disease) are dapsone-sensitive entities.[2]

Eosinophilic cellulitis (Wells syndrome) and eosinophilic annular erythema (EAE) are closely related entities; both involve painful inflammatory and pruritic erythema with tissue eosinophilia. In Wells syndrome, eosinophils usually involve the dermis and the subcutis whereas in EAE, eosinophils are confined to the dermis.[54]

The most recent review of Wells syndrome by Rassler *et al*. concluded that dapsone is a well-tolerated and effective therapy for this syndrome.[55] Many various efficient dose regimens were included in this review. For instance, one could start with dapsone 100 mg daily until remission of the lesions which usually happens after 2 weeks of therapy initiation. Afterward, the dose is reduced by half (50 mg daily) for 6 weeks and finally 50 mg thrice a week.

Pustular diseases

Dapsone has been successfully used in the treatment of various pustular diseases such as acropustulosis of infancy and subcorneal pustular dermatosis (Sneddon-Wilkinson).[2,9] Infantile generalized pustular psoriasis, a rare disease, has been managed with dapsone previously. Two pediatric patients were successfully treated with dapsone. A 7-year-old girl whose pustules and erythema resolved after introduction of oral dapsone 25 mg daily for a total of 5 weeks[56] and a 2-year-old boy with generalized pustular psoriasis treated with oral dapsone 5 mg twice daily.[57] Moreover, in 2016, Sheu *et al*. investigated the use of dapsone in managing both generalized and localized (palmoplantar) pustular psoriasis patients.[58] Four patients were started on oral dapsone (25, 50, 75, or 100 mg daily), and one patient with a localized form was started on topical dapsone 5%. All patients experienced considerable pustule regression and symptomatic amelioration after 1 month of treatment; two patients eventually discontinued the use of systemic immunosuppressants (methotrexate and adalimumab). To date, unfortunately, no consensus on dapsone dosage in the treatment or maintenance of pustular psoriasis is available.

Erosive pustular dermatosis (EPD) is a rare noninfectious disease of the scalp and/or legs of unknown etiology. Clinical findings include a mixture of nonspecific superficial erosions with crusts and pustules on atrophic skin.[59] Several case reports showed tremendous efficacy of dapsone in treating this disease, whether orally or topically. A study in 2017 described the use of oral dapsone 100 mg daily with remarkable clinical improvement after 6 months and a maintenance duration of 3 years with oral dapsone 50 mg.[60] Another study reported the use of oral dapsone 50 mg, twice daily for 1 week, then three times daily for the following weeks. This regimen resulted in a sustained and complete remission of all erosive pustules on the legs, scalp, arms, and tongue of one patient after 6 weeks. Dapsone 50 mg twice daily was eventually continued for an additional 2 months with remission of all lesions in a 12-month follow-up period.[61] On another note, Broussard *et al*. reported higher efficacy of dapsone 5% gel as compared to the oral formulation.[62] In this study, four patients with EPD of the scalp who failed improvement with oral dapsone 100 mg exhibited major improvement within 2 months of initiating dapsone 5% gel twice daily over the scalp. Complete resolution of the dermatosis persisted for at least 4 months with no relapse.

Vasculitis

Dapsone has been implicated as a therapeutic regimen for erythema elevatum diutinum (EED), leukocytoclastic vasculitis, and

urticarial vasculitis.[2,9] One case-series suggested that dapsone 100 mg once daily is the treatment of choice for EED.[63] Furthermore, several studies emerged to show the efficacy and advantage of dapsone in treating giant cell arteritis (GCA). Yates *et al.* conducted a meta-analysis in 2014 to study the efficacy and optimal use of glucocorticoids in GCA.[64] It was observed that dapsone, along with adalimumab, are the only useful corticoid-sparing agents in treating this kind of vasculitis. In addition, dapsone was the single agent associated with decreased risk of infections when compared with corticosteroids. In a retrospective study of 70 patients receiving dapsone as first, second, or third-line treatment for GCA, dapsone combined with glucocorticoids led to a reduction in the daily steroid dose during the first year and a shorter duration of steroid therapy when compared with patients treated with glucocorticoid monotherapy.[65] Finally, Misra *et al.* demonstrated that the use of an average 75 mg daily dose of dapsone during 10 months leads to a higher remission rate of GCA and a lower daily use of prednisone.[66]

Bullous diseases

The advent of dapsone has allowed for more steroid-sparing regimens in managing difficult bullous diseases. Dapsone 50–200 mg daily is effective in the remission induction phase and maintenance phase when treating pemphigus vulgaris.[67–70]

Dapsone has also shown great efficacy in treating other bullous disorders, like IgA pemphigus, linear IgA dermatosis, bullous pemphigoid, mucous membrane pemphigoid, lichen planus pemphigoides, and dermatitis herpetiformis (Duhring's disease).[2,9]

Dapsone is a controversial adjuvant therapeutic regimen for the treatment of pemphigoid gestationis (formerly known as herpes gestationis or pemphigus herpetiformis).[71,72] It is used postpartum since it is classified as pregnancy category C in the United States.[71] For the best outcome, a dosage of 50–150 mg daily administered orally is recommended with azathioprine and plasmapheresis when systemic corticosteroids are not sufficient.

Many studies report the use of dapsone as the most common adjuvant drug to systemic steroids in the treatment of resistant pemphigus foliaceus.[73–76] Doses of oral dapsone ranging from 25 to 300 mg daily in combination with systemic corticosteroids at a dose of 1 mg/kg/day were associated with excellent response. The combination of steroids with dapsone was superior to that of azathioprine with steroids.[75] Furthermore, when neutrophilic pustules are prominent in pemphigus foliaceus, dapsone is the best adjuvant treatment to reduce the prominent neutrophilic infiltrate.[74] Nonetheless, a case of eosinophilic pneumonia induced by dapsone while treating pemphigus foliaceus has been reported in the literature.[77] Thus, it is crucial to properly monitor patients undergoing therapy with dapsone, whether as a monotherapy or as part of a combination regimen.

Several cases reported successful remission of the vegetating lesions seen in pemphigus vegetans after adding dapsone 50–100 mg daily[78,79] to oral systemic steroids. Dapsone should be tapered and sustained in the maintenance phase, along with tapered systemic steroids, because of its ability to prevent eosinophilic spongiosis, usually seen in pemphigus lesions.[80]

Genetic diseases

Benign familial chronic pemphigus, or Hailey–Hailey disease, is an autosomal dominant disorder caused by a mutation in the ATP2C1 gene, resulting in blisters and erosions in the intertriginous areas.[81] Many treatments have been offered to manage this erosive dermatosis, ranging from topical corticosteroids or immunosuppressants as 5-fluorouracil to systemic therapies such as dapsone.[82] One study in 1971 reported successful treatment of Hailey-Hailey with dapsone in three patients.[83] One of the patients was started on dapsone 200 mg daily with resolution of pruritus within 2 days and eventual resolution of lesions within 2 weeks of a 100 mg daily maintenance dose. The other two patients were started on dapsone 100 mg, which led to

Table 1 Local and systemic adverse effects of dapsone

Dermatologic	Hematological	Gastrointestinal	Renal	Cardiac	Neurologic
Exfoliative dermatitis	Methemoglobinemia	Nausea/vomiting	Albuminuria	Atrioventricular block	Peripheral neuropathy
Erythema multiforme	G6PD-induced hemolytic anemia	Anorexia	Electrolyte imbalance		Blindness
Erythema nodosum	Agranulocytosis	Abdominal pain			Insomnia
Urticaria		LFTs nonspecific abnormalities			Psychosis
Erythema morbilliform		Prehepatic jaundice			
Scarlatiniform exanthema		Cholestatic hepatitis			
Toxic epidermal necrolysis		Hepatic coma			
Photosensitivity					
Rash in AIDS patients					
Fixed drug eruption					

LFTs, liver function tests.

resolution of pruritus and eventual significant improvement in lesion severity with 50 mg daily maintenance dose after 2 weeks. One of these patients had to stop dapsone because of a decrease in hematocrit, however, she remained asymptomatic for 1 year.

Miscellaneous

Dapsone has been used for the treatment of dermatological and nondermatological miscellaneous diseases. Dapsone is highly efficient in treating brown recluse spider bite (loxoscelism).[84] The spider bite causes damage by activating membrane phospholipids. The success of dapsone in treating loxoscelism and decreasing the need for surgery is attributed to its antineutrophilic effects.[2] In addition, studies suggest that combining dapsone with an antivenom may yield better results since they have independent mechanisms of action.[85] Corticosteroids would be then used when systemic symptoms appear.

Of note, dapsone is also used in treating idiopathic thrombocytopenic purpura.[86]

Adverse effects

Dapsone is associated with local and systemic side effects affecting various organs including, but not limited to, the hematologic system, the gastrointestinal system, and the skin (cf. Table 1).[2,9]

Dapsone hypersensitivity syndrome is a dose independent late-onset life-threatening hypersensitivity reaction after dapsone initiation. It occurs in 0.5–3.6% of patients treated with dapsone and has similar features of drug reaction with

Table 2 Most common drug interactions with dapsone

Drug/value	Class	Interaction with dapsone	Level of interaction	Comments about combination	Drug compendium
Didanosine	Reverse-transcriptase inhibitor	Increase in dapsone toxicity	Closely monitor patient	May increase risk of nerve damage	USP DI AHFS[91]
Pyrimethamine	Antiparasitic folic acid antagonist	Additive drug effects	Minor	May cause low blood cell counts	GenRx PDR AHFS[91]
Hemolytic drugs[a]	–	Additive drug effects	–	Increases destruction of RBCs	AHFS[91]
Rifampin	Antimycobacterial	Decrease in dapsone level or effect	Closely monitor patient	Alters metabolism of dapsone	USP DI GenRx PDR AHFS[91]
Trimethoprim	Pyrimidine inhibitor of dihydrofolate reductase	Increase in dapsone blood levels	Moderate	Impairs bone marrow function, causes hemolysis and methemoglobinemia	USP DI GenRx PDR AHFS[95]
Probenecid	Uricosuric	Increase in dapsone blood levels	Moderate	May cause bluish skin discoloration	AHFS[91]
Clarithromycin	Macrolide	Increase in dapsone blood levels	Closely monitor patient	May cause decreased effect of clarithromycin and disease relapse	Case report[96]
Fluconazole, Voriconazole	Azole antifungals	Decrease in dapsone toxicity	–	Azoles inhibiting CYP2C9 or CYP2C19 may lead to a reduction in dapsone toxicities (CYP450 inducers may have increased toxicity)	Review[97,98]
Vorinostat	Histone deacetylase inhibitor	–	–	Severe hemolytic anemia requiring several transfusions	Case report[98]
Warfarin	Anticoagulant	Increase in warfarin effect	–	Supratherapeutic INR	Case report[99]
Topical BP	Antibiotic	–	–	Skin discoloration when mixed. Use at different times of the day and wash off before applying any other topical agent	Original article[100]
HbA1c value	Used to monitor diabetes	False lowering of HbA1c and inappropriate monitoring of diabetes	–	Dapsone causes hemolytic anemia and shortens the lifespan of RBCs, hence inaccurately lowers HbA1c	Case report[101]

[a]Hemolytic drugs include nitrite, aniline, phenylhydrazine, naphthalene, niridazole, primaquine, or nitrofurantoin.
AHFS, American Hospital Formulary Service; BP, benzoyl peroxide; DI, Drug Information; GenRx, Generic Drug List; HbA1c, hemoglobin A1c; INR, International Normalized Ratio; PDR, Physicians' Desk Reference; RBCs, red blood cells ; USP, United States Pharmacopeia.

eosinophilia and systemic symptoms.[87] A systemic review and meta-analysis by Tangamornsuksan and Lohitnavy proved the association between this syndrome and HLA-B*1301[88] which has been found to be more prevalent in the Chinese and Southeast Asian population.[89] However, further studies to assess the importance of screening for this allele in these particular populations are warranted. Furthermore, Yue *et al.* identified five nucleotide polymorphisms in the HLA-DRB1 that are significantly associated with dapsone hypersensitivity reaction (positions 133, 142, −17, 11, and 13).[90]

Drug interactions

Dapsone is a widely prescribed drug off-label in dermatology. It is inevitable to study its interaction with other drugs, especially for patients with multiple comorbidities.

A review by Chao and Maibach took interest in reporting the lack of conformity in commonly used drug compendia for selected at-risk dermatologic drugs, including dapsone.[91] They found that dapsone interacted with a variety of drugs while collecting and comparing data using drug monographs from four highly used drug compendia in the United States: Mosby's GenRx, USP (United States Pharmacopeia) Drug Information, AHFS (American Hospital Formulary Service) Drug Information, and the Physicians' Desk Reference. However, these four references did not agree on all drug interactions of dapsone. Plus, this review did not include the nature of clinically relevant drug–drug interactions and algorithms. Nonetheless, one can always look into the literature and into various case-reports to document possible interactions.

We report some of the most important drugs interacting with dapsone and their resultant effects in Table 2. Consequently, it would be important for dermatologists to focus on a detailed drug history given the frequent use of such drugs in managing common dermatologic diseases.

Future prospects

Dapsone is a multipurpose drug with a wide variety of benefits, especially in dermatology. Interestingly, given that it belongs to the sulfone family, not only does it possess antibacterial properties, but it could also have antiaging properties. In a study by Cho *et al.*, the use of 4,4'-diaminodiphenylsulfone (dapsone) was shown to extend the organismic lifespan in *Caenorhabditis elegans*.[92] This model showed that dapsone treatment led to a delay in aging, lowered oxygen consumption rate, and decreased mitochondrial damage. These findings imply the potential use of dapsone in lowering reactive oxygen species and, more importantly, its conceivable effect on human lifespan extension. Finally, dapsone has been shown to be protective in several disorders such as recovery post-ischemic stroke.[93,94] Zhan *et al.* demonstrated that dapsone has protective effects on brain microvessels by decreasing the destruction of tight junction within endothelial cells. Given its antiaging and neuroprotective properties, dapsone has an immense potential to promote healthier and longer living. Future studies are warranted to investigate dapsone's role as an anti-inflammatory, antioxidant, and possibly antineoplastic drug.

References

1 Doull JA. Sulfone therapy of leprosy. Background, early history and present status. *Int J Lepr* 1963; **31**: 143–160.
2 Wozel G, Blasum C. Dapsone in dermatology and beyond. *Arch Dermatol Res* 2014; **306**: 103–124.
3 Wittmann J. Derivate desp-Nitrothiophenols. *Eur J Inorg Chem* 1908: 2264.
4 Buttle GAH, Stephenson D, Smith S, *et al.* The treatment of streptococcal infections in mice with 4:4'diaminophenylsulphone. *Lancet* 1937; **229**: 1331–1334.
5 Debol SM, Herron MJ, Nelson RD. Anti-inflammatory action of dapsone: inhibition of neutrophil adherence is associated with inhibition of chemoattractant-induced signal transduction. *J Leukoc Biol* 1997; **62**: 827–836.
6 Fourneau E, Trefouel J, Nitti F, *et al.* Action anti-streptococcique des derives sulfures organiques. *Comptes rendus de l'Académie des Sciences* 1937; **204**: 1763–1766.
7 Esteves J, Brandao FN. Acerca da accao das sulfamidas e das sulfonas na doenca de Duhring. *Trab Soc Portuguesa Dermatol Venereol* 1950; **8**: 209–217.
8 Sneddon IB, Wilkinson DS. Subcorneal pustular dermatosis. *Br J Dermatol* 1979; **100**: 61–68.
9 Wozel VE. Innovative use of dapsone. *Dermatol Clin* 2010; **28**: 599–610.
10 Coleman MD. Dapsone: modes of action, toxicity and possible strategies for increasing patient tolerance. *Br J Dermatol* 1993; **129**: 507–513.
11 Webster GF, Alexander JC, McArthur WP, *et al.* Inhibition of chemiluminescence in human neutrophils by dapsone. *Br J Dermatol* 1984; **110**: 657–663.
12 Booth SA, Moody CE, Dahl MV, *et al.* Dapsone suppresses integrin-mediated neutrophil adherence function. *J Invest Dermatol* 1992; **98**: 135–140.
13 Kanoh S, Tanabe T, Rubin BK. Dapsone inhibits IL-8 secretion from human bronchial epithelial cells stimulated with lipopolysaccharide and resolves airway inflammation in the ferret. *Chest* 2011; **140**: 980–990.
14 Wozel G, Lehmann B. Dapsone inhibits the generation of 5-lipoxygenase products in human polymorphonuclear leukocytes. *Skin Pharmacol Physiol* 1995; **8**: 196–202.
15 Bozeman PM, Learn DB, Thomas EL. Inhibition of the human leukocyte enzymes myeloperoxidase and eosinophil peroxidase by dapsone. *Biochem Pharmacol* 1992; **44**: 553–563.
16 Hashimoto K, Singer K, Lazarus GS. The effect of corticosteroids, dapsone and gold upon plasminogen activator synthesis and secretion by human epidermal cells cultured with pemphigus antibody. *Br J Dermatol* 1984; **110**: 293–297.
17 Kurien G, Jamil RT, Preuss CV. *Dapsone*. StatPearls [Internet]: Treasure Island, FL: StatPearls Publishing, 2019.
18 Pickert A, Raimer S. An evaluation of dapsone gel 5% in the treatment of acne vulgaris. *Expert Opin Pharmacother* 2009; **10**: 1515–1521.
19 Fischer M. Leprosy – an overview of clinical features, diagnosis, and treatment. *J Dtsch Dermatol Ges* 2017; **15**: 801–827.

20 Sener O, Doganci L, Safali M, *et al*. Severe dapsone hypersensitivity syndrome. *J Investig Allergol Clin Immunol* 2006; **16**: 268–270.
21 Karpati S. Dermatitis herpetiformis. *Clin Dermatol* 2012; **30**: 56–59.
22 Antiga E, Caproni M. The diagnosis and treatment of dermatitis herpetiformis. *Clin Cosmet Investig Dermatol* 2015; **8**: 257–265.
23 Keri J. What's new in acne and rosacea? *Semin Cutan Med Surg* 2016; **35**: 103–106.
24 Administration UFaD. Aczone (dapsone topical gel) 5 percent safety; labeling changes approved by FDA center for drug evaluation and research. 2016.
25 Sardana K, Gupta T, Garg VK, *et al*. Antibiotic resistance to *Propionobacterium acnes*: worldwide scenario, diagnosis and management. *Expert Rev Anti Infect Ther* 2015; **13**: 883–896.
26 Zhanel GG, Del Rosso JQ. Activity of dapsone versus community and hospital pathogens from the CANWARD study. *J Clin Aesthet Dermatol* 2016; **9**: 42–47.
27 Allergan Inc. Aczone (dapsone) gel, 7.5%, for topical use: US prescribing information. 2016.
28 Al-Salama ZT, Deeks ED. Dapsone 7.5% gel: a review in acne vulgaris. *Am J Clin Dermatol* 2017; **18**: 139–145.
29 Didona D, Paolino G, Donati P, *et al*. Resolution of nodulocystic acne with oral dapsone. *Dermatol Ther* 2017; **30**: e12406.
30 Wakabayashi M, Fujii N, Fujimoto N, *et al*. Usefulness of dapsone for the treatment of Asian severe acne. *J Dermatol* 2013; **40**: 502–504.
31 Basavaraju A. Toxoplasmosis in HIV infection: an overview. *Trop Parasitol* 2016; **6**: 129–135.
32 World Health Organization. Review of the safety of chlorproguanil-dapsone in the treatment of uncomplicated falciparum malaria in Africa: report of a technical consultation convened by WHO, Geneva. 2005.
33 Poirot E, Vittinghoff E, Ishengoma D, *et al*. Risks of hemolysis in glucose-6-phosphate dehydrogenase deficient infants exposed to chlorproguanil-dapsone, mefloquine and sulfadoxine-pyrimethamine as part of intermittent presumptive treatment of malaria in infants. *PLoS ONE* 2015; **10**: e0142414.
34 Enwere O, Falade C Haematological response following treatment with chlorproguanil/dapsone or sulfadoxine/pyrimethamine for acute uncomplicated malaria in Nigerian children. *Int J Infect Trop Dis* 2015; **2**: 48–55.
35 Andersen RK, Jemec GB. Treatments for hidradenitis suppurativa. *Clin Dermatol* 2017; **35**: 218–224.
36 Deckers IE, Prens EP. An update on medical treatment options for hidradenitis suppurativa. *Drugs* 2016; **76**: 215–229.
37 Kaur MR, Lewis HM. Hidradenitis suppurativa treated with dapsone: a case series of five patients. *J Dermatol Treat* 2006; **17**: 211–213.
38 Yazdanyar S, Boer J, Ingvarsson G, *et al*. Dapsone therapy for hidradenitis suppurativa: a series of 24 patients. *Dermatology* 2011; **222**: 342–346.
39 Staub J, Pfannschmidt N, Strohal R, *et al*. Successful treatment of PASH syndrome with infliximab, cyclosporine and dapsone. *J Eur Acad Dermatol Venereol* 2015; **29**: 2243–2247.
40 Khandalavala BN. A disease-modifying approach for advanced hidradenitis suppurativa (regimen with metformin, liraglutide, dapsone, and finasteride): a case report. *Case Rep Dermatol* 2017; **9**: 70–78.
41 Scheinfeld N. Dissecting cellulitis (Perifolliculitis Capitis Abscedens et Suffodiens): a comprehensive review focusing on new treatments and findings of the last decade with commentary comparing the therapies and causes of dissecting cellulitis to hidradenitis suppurativa. *Dermatol Online J* 2014; **20**: 22692.
42 Lara Rivero A, Whitfeld M. An update on the treatment of rosacea. *Aust Prescr* 2018; **41**: 20–24.
43 Faghihi G, Khosravani P, Nilforoushzadeh MA, *et al*. Dapsone gel in the treatment of papulopustular rosacea: a double-blind randomized clinical trial. *J Drugs Dermatol* 2015; **14**: 602–606.
44 Kassardjian M, Patel M, Shitabata P, *et al*. Management of periocular granuloma annulare using topical dapsone. *J Clin Aesthet Dermatol* 2015; **8**: 48–51.
45 Lukacs J, Schliemann S, Elsner P. Treatment of generalized granuloma annulare – a systematic review. *J Eur Acad Dermatol Venereol* 2015; **29**: 1467–1480.
46 El Benaye J, Oumakhir S, Ghfir M, *et al*. Efficacité de la dapsone dans deux cas de lupus miliaire disséminé de la face. *Annales de Dermatologie et de Vénéréologie* 2011; **138**: 597–600.
47 Sardana K, Chugh S, Ranjan R, *et al*. Lupus miliaris disseminatus faciei: a resistant case with response to cyclosporine. *Dermatol Ther* 2017; **30**: e12496.
48 Grattagliano I, Bonfrate L, Ruggiero V, *et al*. Novel therapeutics for the treatment of familial Mediterranean fever: from colchicine to biologics. *Clin Pharmacol Ther* 2014; **95**: 89–97.
49 Salehzadeh F, Jahangiri S, Mohammadi E. Dapsone as an alternative therapy in children with familial Mediterranean fever. *Iran J Pediatr* 2012; **22**: 23–27.
50 Bhat RM, Nandakishore B, Sequeira FF, *et al*. Pyoderma gangrenosum: an Indian perspective. *Clin Exp Dermatol* 2011; **36**: 242–247.
51 Pereira N, Brites MM, Goncalo M, *et al*. Pyoderma gangrenosum – a review of 24 cases observed over 10 years. *Int J Dermatol* 2013; **52**: 938–945.
52 Braswell SF, Kostopoulos TC, Ortega-Loayza AG. Pathophysiology of pyoderma gangrenosum (PG): an updated review. *J Am Acad Dermatol* 2015; **73**: 691–698.
53 Din RS, Tsiaras WG, Li DG, *et al*. Efficacy of systemic dapsone treatment for pyoderma gangrenosum: a retrospective review. *J Drugs Dermatol* 2018; **17**: 1058–1060.
54 Nakazato S, Fujita Y, Shinkuma S, *et al*. Eosinophilic annular erythema is clinically characterized by central pigmentation reflecting basal melanosis: a clinicopathological study of 10 cases. *J Eur Acad Dermatol Venereol* 2017; **31**: 1916–1923.
55 Rassler F, Lukacs J, Elsner P. Treatment of eosinophilic cellulitis (Wells syndrome) – a systematic review. *J Eur Acad Dermatol Venereol* 2016; **30**: 1465–1479.
56 Yu HJ, Park JW, Park JM, *et al*. A case of childhood generalized pustular psoriasis treated with dapsone. *J Dermatol* 2001; **28**: 316–319.
57 Chaves YN, Cardoso DN, Jorge PF, *et al*. Childhood pustular psoriasis: case report. *An Bras Dermatol* 2010; **85**: 899–902.
58 Sheu JS, Divito SJ, Enamandram M, *et al*. Dapsone therapy for pustular psoriasis: case series and review of the literature. *Dermatology* 2016; **232**: 97–101.
59 Semkova K, Tchernev G, Wollina U. Erosive pustular dermatosis (chronic atrophic dermatosis of the scalp and extremities). *Clin Cosmet Investig Dermatol* 2013; **6**: 177–182.
60 Mervak JE, Gan SD, Smith EH, *et al*. Facial erosive pustular dermatosis after cosmetic resurfacing. *JAMA Dermatol* 2017; **153**: 1021–1025.
61 Feramisco JD, Goerge T, Schulz SE, *et al*. Disseminated erosive pustular dermatosis also involving the mucosa: successful treatment with oral dapsone. *Acta Derm Venereol* 2012; **92**: 91–92.

62 Broussard KC, Berger TG, Rosenblum M, *et al*. Erosive pustular dermatosis of the scalp: a review with a focus on dapsone therapy. *J Am Acad Dermatol* 2012; **66**: 680–686.
63 Wilkinson SM, English JSC, Smith NP, *et al*. Erythema elevatum diutinum: a clinicopathological study. *Clin Exp Dermatol* 1992; **17**: 87–93.
64 Yates M, Loke YK, Watts RA, *et al*. Prednisolone combined with adjunctive immunosuppression is not superior to prednisolone alone in terms of efficacy and safety in giant cell arteritis: meta-analysis. *Clin Rheumatol* 2014; **33**: 227–236.
65 Ly KH, Dalmay F, Gondran G, *et al*. Steroid-sparing effect and toxicity of dapsone treatment in giant cell arteritis: a single-center, retrospective study of 70 patients. *Medicine.* 2016; **95**: e4974.
66 Misra DP, Sharma A, Kadhiravan T, *et al*. A scoping review of the use of non-biologic disease modifying anti-rheumatic drugs in the management of large vessel vasculitis. *Autoimmun Rev* 2017; **16**: 179–191.
67 Baum S, Debby A, Gilboa S, *et al*. Efficacy of dapsone in the treatment of pemphigus vulgaris: a single-center case study. *Dermatology* 2016; **232**: 578–585.
68 Gürcan HM, Ahmed AR. Efficacy of dapsone in the treatment of pemphigus and pemphigoid. *Am J Clin Dermatol* 2009; **10**: 383–396.
69 Quaresma MV, Bernardes Filho F, Hezel J, *et al*. Dapsone in the treatment of pemphigus vulgaris: adverse effects and its importance as a corticosteroid sparing agent. *An Bras Dermatol* 2015; **90**(3 suppl 1): 51–54.
70 Werth VP, Fivenson D, Pandya AG, *et al*. Multicenter randomized, double-blind, placebo-controlled, clinical trial of dapsone as a glucocorticoid-sparing agent in maintenance-phase pemphigus vulgaris. *Arch Dermatol* 2008; **144**: 25–32.
71 Intong LR, Murrell DF. Pemphigoid gestationis: current management. *Dermatol Clin* 2011; **29**: 621–628.
72 Santos-Alarcon S, Benavente-Villegas C, Garcia-Briz I, *et al*. Urticarial lesions in a pregnant woman. *Acta Dermatovener CR* 2018; **26**: 71–72.
73 Garcia-Melendez ME, Eichelmann K, Salas-Alanis JC, *et al*. Pemphigus foliaceus in an 11-year-old mexican girl with response to oral dapsone. *Case Rep Pediatr* 2013; **2013**: 291256.
74 Mendez-Flores S, Avalos-Diaz E, Dominguez-Cherit J, *et al*. Pemphigus foliaceus with circinated plaques and neutrophil pustules. *J Cutan Pathol* 2016; **43**: 1062–1066.
75 Pires CA, Viana VB, Araujo FC, *et al*. Evaluation of cases of pemphigus vulgaris and pemphigus foliaceus from a reference service in Para state, Brazil. *An Bras Dermatol.* 2014; **89**: 556–561.
76 Tavakolpour S. Current and future treatment options for pemphigus: Is it time to move towards more effective treatments? *Int Immunopharmacol* 2017; **53**: 133–142.
77 Endo H, Fukuda H, Yokouchi Y, *et al*. Diaminodiphenyl sulfone-induced eosinophilic pneumonia in a patient with pemphigus foliaceus. *Eur J Dermatol* 2015; **25**: 267–268.
78 Apalla Z, Sotiriou E, Lazaridou E, *et al*. Pemphigus vegetans of the tongue: a diagnostic and therapeutic challenge. *Int J Dermatol* 2013; **52**: 350–351.
79 Khatib Y, Makhija M, Patel RD, *et al*. Pemphigoid vegetans in childhood: a case report and short review of literature. *Indian J Dermatol* 2015; **60**: 422.
80 Son YM, Kang HK, Yun JH, *et al*. The neumann type of pemphigus vegetans treated with combination of dapsone and steroid. *Ann Dermatol* 2011; **23**(suppl 3): S310–S313.
81 Arora H, Bray FN, Cervantes J, *et al*. Management of familial benign chronic pemphigus. *Clin Cosmet Investig Dermatol* 2016; **9**: 281–290.
82 Nanda KB, Saldanha CS, Jacintha M, *et al*. Hailey-hailey disease responding to thalidomide. *Indian J Dermatol* 2014; **59**: 190–192.
83 Sire DJ, Johnson BL. Benign familial chronic pemphigus treated with dapsone. *Arch Dermatol* 1971; **103**: 262–265.
84 Zhu YI, Stiller MJ. Dapsone and sulfones in dermatology: overview and update. *J Am Acad Dermatol* 2001; **45**: 420–434.
85 Rees R, Campbell D, Rieger E, *et al*. The diagnosis and treatment of brown recluse spider bites. *Ann Emerg Med* 1987; **16**: 945–949.
86 Song J. Dapsone therapy for immune thrombocytopenic purpura: old but still unfamiliar. *Blood Res* 2017; **52**: 77–78.
87 Adwan MH. Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome and the rheumatologist. *Curr Rheumatol Rep* 2017; **19**: 3.
88 Tangamornsuksan W, Lohitnavy M. Association between HLA-B*1301 and dapsone-induced cutaneous adverse drug reactions: a systematic review and meta-analysis. *JAMA Dermatol* 2018; **154**: 441–446.
89 Gonzalez-Galarza FF, Takeshita LY, Santos EJ, *et al*. Allele frequency net 2015 update: new features for HLA epitopes, KIR and disease and HLA adverse drug reaction associations. *Nucleic Acids Res* 2015; **43**(D1): D784–D788.
90 Yue Z, Sun Y, Wang C, *et al*. Amino acid variants of HLA-DRB1 confer susceptibility to dapsone hypersensitivity syndrome in addition to HLA-B*13:01. *J Invest Dermatol* 2018; **138**: 1101–1106.
91 Chao SD, Maibach HI. Lack of drug interaction conformity in commonly used drug compendia for selected at-risk dermatologic drugs. *Am J Clin Dermatol* 2005; **6**: 105–111.
92 Cho SC, Park MC, Keam B, *et al*. DDS, 4,4′-diaminodiphenylsulfone, extends organismic lifespan. *Proc Natl Acad Sci USA* 2010; **107**: 19326–19331.
93 Chui DH, Tabira T, Izumi S, *et al*. Decreased beta-amyloid and increased abnormal Tau deposition in the brain of aged patients with leprosy. *Am J Pathol* 1994; **145**: 771–775.
94 Lee SW, Kim WJ, Choi YK, *et al*. SSeCKS regulates angiogenesis and tight junction formation in blood-brain barrier. *Nat Med* 2003; **9**: 900–906.
95 Corallo C, Coutsouvelis J, Avery S, *et al*. Dapsone and azole interactions: a clinical perspective. *J Oncol Pharm Pract* 2018; **24**: 637–640.
96 Lewis JA, Petty WJ, Harmon M, *et al*. Hemolytic anemia in two patients with glioblastoma multiforme: a possible interaction between vorinostat and dapsone. *J Oncol Pharm Pract* 2015; **21**: 220–223.
97 Lee BL, Medina I, Benowitz NL, *et al*. Dapsone, trimethoprim, and sulfamethoxazole plasma levels during treatment of Pneumocystis pneumonia in patients with the acquired immunodeficiency syndrome (AIDS). Evidence of drug interactions. *Ann Intern Med* 1989; **110**: 606–611.
98 Gallien S, Bige N, Kitzis MD, *et al*. Drug-to-drug interaction between dapsone and minocycline: an unusual cause of relapse of toxoplasmic encephalitis in an HIV-infected patient. *Scand J Infect Dis* 2009; **41**: 700–702.
99 Truong T, Haley J. Probable warfarin and dapsone interaction. *Clin Appl Thromb-Hem* 2012; **18**: 107–109.
100 Dubina MI, Fleischer AB Jr. Interaction of topical sulfacetamide and topical dapsone with benzoyl peroxide. *Arch Dermatol* 2009; **145**: 1027–1029.
101 Roxby A, Jain R. Dapsone interferes with hemoglobin A1c monitoring of diabetes in an HIV-infected patient. *AIDS* 2013; **27**: 299–301.

