

# Dermatological pharmacology: systemic drugs

Sarah Wakelin

## Abstract

In recent years there has been an evolution in the systemic therapy of skin disease, in particular immunosuppressive agents, retinoids and, most lately, biological drugs and new classes of drugs for advanced skin cancer. Developments in drug monitoring include measurement of thiopurine methyl transferase enzyme activity before prescribing azathioprine, to screen for patients at risk of severe bone marrow depression, and monitoring recipients of methotrexate with procollagen III peptide or Fibroscans to detect hepatic fibrosis. Biologics including anti-tumour necrosis factor  $\alpha$  therapy offer a new and effective treatment for severe psoriasis in patients who have failed to respond to conventional systemic drugs, but risks include reactivation of tuberculosis. Oral retinoid therapy has expanded to include alitretinoin, a new oral drug for severe hand eczema, and stringent requirements have been introduced for females treated with isotretinoin due to the high risk of birth deformity which is common to these drugs. It is important that physicians are aware of the adverse effects of treatment and that patients are carefully selected screened and monitored to minimize any risk.

**Keywords** advanced skin malignancy; biologics; dermatoses; drug monitoring; immunosuppressive; psoriasis; quality of life; retinoids; systemic therapy

## Introduction

Most patients with common inflammatory dermatoses such as eczema and psoriasis can be treated effectively with topical agents or phototherapy. However, a minority with severe disease require potent systemic therapy for disease control. These drugs can improve quality of life, but carry a risk of serious adverse effects, especially in those with co-morbidities or underlying infection. Systemic drugs are also important in treating rarer dermatoses that are debilitating or potentially life-threatening, including immunobullous diseases, neutrophilic dermatoses, connective tissue diseases and vasculitides. Their use in these diseases is often outside the drug's licensed indications and lacking in a high level of clinical evidence.

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## What's new?

- Anti-tumour necrosis factor and anti-interleukin-12/interleukin-23 biological drugs for the treatment of severe psoriasis
- Alitretinoin, a new oral retinoid for severe chronic hand eczema
- Pre-treatment measurement of thiopurine methyl transferase activity for azathioprine
- Non-invasive monitoring for methotrexate hepatotoxicity including serial procollagen III peptide concentrations and Fibroscans
- Mandatory pregnancy prevention plan for use of oral isotretinoin in females
- Vemurafenib for metastatic melanoma
- Vismodegib for advanced basal cell carcinoma

## Immunosuppressives

Several drugs that were first used to prevent organ transplant rejection have found an established role in dermatology. The synthetic purine analogue, **azathioprine**, is licensed for the treatment of pemphigus vulgaris, systemic lupus erythematosus and dermatomyositis/polymyositis. It is also an effective monotherapy in severe atopic eczema and chronic actinic dermatitis, and is often used as a corticosteroid-sparing drug in the autoimmune blistering disease, bullous pemphigoid (Figure 1). One of the most serious adverse effects of azathioprine is neutropenia. Pre-treatment screening for deficiencies of the enzyme thiopurine methyl transferase (TPMT), which plays a key role in the metabolism of azathioprine, identifies the majority of patients at risk of bone marrow depression. This is now a recommended baseline investigation and can also be used as a guide to drug dosage in those with low or high enzyme activity (Table 1).<sup>1</sup>

Ciclosporin, the original calcineurin inhibitor, has been licensed for several decades as a short-term treatment of severe atopic eczema (up to 8 weeks) and for severe psoriasis (Figure 2). It is used in doses of 2.5–3 mg/kg/day, escalated to 5 mg/kg/day when rapid disease control is necessary. The main adverse effects are hypertension and nephrotoxicity, especially with long-term treatment. Generic formulations have become available recently but prescribers should not switch randomly between brands, to avoid potential differences in bioavailability.

The newer lymphocyte-selective immunosuppressant, mycophenolate mofetil, has also been used with benefit in dermatology, but is unlicensed due to a lack of large clinical trials. Its main use is as a corticosteroid-sparing drug in immunobullous diseases, connective tissue diseases and vasculitides.<sup>2</sup> Likewise, the antilymphocyte monoclonal antibody, rituximab (anti-CD20 antibody), which is licensed for treatment of haematological malignancies and severe rheumatoid arthritis, is an effective treatment for severe autoimmune blistering diseases.<sup>3</sup> An important adverse effect of these drugs is the increased risk of infections – common and atypical/opportunistic – which may be life-threatening, including isolated reports of progressive multifocal leukoencephalopathy (PML) due to reactivation of JC polyoma virus.<sup>4</sup>

Before commencing immunosuppressive therapy, patients should be screened for chronic hepatitis B virus and HIV infection.



**Figure 1** Bullous pemphigoid – an autoimmune blistering disease (Courtesy of Manson Publishing Ltd, from Rycroft, Robertson and Wakelin: Dermatology, 2nd Edn – A Colour Handbook, ISBN 978-1-84076-110-8).



**Figure 2** Severe chronic plaque psoriasis requiring systemic therapy (Courtesy of Manson Publishing Ltd, from Rycroft, Robertson and Wakelin: Dermatology, 2nd Edn – A Colour Handbook, ISBN 978-1-84076-110-8).

Active infection is not an absolute contraindication to treatment but requires the shared expertise of relevant physicians (hepatology/infectious disease). Long-term immunosuppressive therapy also carries an increased risk of malignancy, especially lymphomas

**Thiopurine methyl transferase (TPMT) testing and azathioprine toxicity<sup>1</sup>**

- Baseline testing predicts severe neutropenia in patients with absent TPMT activity
- Intermediate TPMT activity is associated with myelotoxicity in patients receiving conventional azathioprine doses
- Baseline testing does not identify all individuals at risk of haematological toxicity so continued monitoring of blood counts is necessary
- Patients with absent TPMT activity are unsuitable for azathioprine
- The recommended daily maintenance dose in those with intermediate TPMT activity is 1.0–1.5 mg/kg
- The recommended daily maintenance dose in those with normal TPMT activity is 2.0–3.0 mg/kg

**Table 1**

and skin cancer. The latter is a particular consideration in patients who have had previous excess sun exposure or ultraviolet (UV) therapy treatment, especially psoralen UVA ('PUVA'), which predispose them to skin cancer development.<sup>5</sup>

**Antimetabolites and cytotoxics**

**Methotrexate (MTX)**, given once weekly at low dose, is an effective treatment of moderate to severe plaque psoriasis and the 'gold standard' against which newer drugs are compared. MTX is also effective in the treatment of psoriatic arthritis and can be combined with biologicals (see below). Concomitant use of folic acid improves tolerability (reducing nausea and gastrointestinal adverse effects). The main concern amongst psoriasis sufferers is hepatic fibrosis. Patients with type 2 diabetes mellitus and obesity are at significantly increased risk, whilst the risk associated with alcohol consumption and hepatitis B and C is less clear.<sup>6</sup> New non-invasive methods of monitoring liver toxicity including serial measurement of serum type III procollagen aminopeptide and transient elastography (Fibroscan<sup>®</sup>) have largely replaced the need for routine liver biopsies (Table 2).

### Methotrexate and monitoring for hepatotoxicity

- Pre-existing risk factors include obesity (common in psoriasis patients) and type 2 diabetes mellitus
- Use standard liver function tests and serial serum procollagen III concentration
- Procollagen III concentration may be unreliable in people with psoriatic arthritis and cannot be used in children and young people
- The estimated positive predictive value is 23–95% and the estimated negative predictive value is 89–100%

**Table 2**

The antineoplastic drug, cyclophosphamide, is not licensed for use in skin disease with the exception of advanced mycosis fungoides (cutaneous T cell lymphoma), but is occasionally used in conjunction with systemic corticosteroids in the treatment of severe immunobullous diseases and refractory cutaneous vasculitides.

### Glucocorticosteroids and anti-allergic therapy

Oral glucocorticosteroids continue to play an important role in the short-term management of acute severe inflammatory and allergic skin diseases, including eczema, urticaria/angioedema, immunobullous diseases, vasculitis, neutrophilic dermatoses (pyoderma gangrenosum and Sweet's syndrome), connective tissue diseases and severe cutaneous adverse drug reactions. However, their long-term use carries the risk of numerous complications and the decision to continue treatment needs to be carefully balanced against risk.

### Antihistamines

Newer (third generation) non-sedating antihistamines are routinely used to treat all forms of urticaria and have an excellent long-term safety record. Recent guidelines support their use in high doses ('up-dosing') in patients with chronic urticaria who do not respond to conventional dosages.<sup>7</sup> The monoclonal antibody, omalizumab, indicated for severe asthma, is also a highly effective therapy for chronic spontaneous urticaria<sup>8</sup> but is currently unlicensed for use in skin disease.

### Oral retinoids

The synthetic retinoids are vitamin A derivatives with wide-ranging effects on cell growth and differentiation and the innate immune system. Oral isotretinoin (9-*cis*-retinoic acid) has unparalleled effectiveness in the treatment of acne and is indicated in patients with severe disease, scarring and psychological upset. Common adverse effects include dryness of the skin and mucous membranes. Mood change, depression and suicide have been reported in association with treatment. Whereas it is possible that these represent a rare idiosyncratic drug reaction, it should be remembered that acne itself is associated with low self-esteem and depression. Physicians prescribing isotretinoin should therefore monitor patients carefully for psychological symptoms (Goodfield).

**Acitretin** is an established treatment for psoriasis, Darier's disease and severe congenital ichthyosis. Although less effective than other systemic psoriasis therapy, it is useful in patients with a history of internal malignancy or underlying HIV infection as it lacks immunosuppressive effects. There is also increasing evidence that it may be of benefit in prophylaxis of non-melanoma skin cancer in organ transplant recipients and those with severe sun damage.<sup>9</sup>

The newest oral retinoid in dermatology is alitretinoin. A large placebo-controlled trial has shown it to be very effective in the treatment of severe chronic hand eczema.<sup>10</sup> Alitretinoin's precise mechanism of action is unclear, but it has a range of immunomodulatory actions that may be of clinical relevance.

All oral retinoids are powerful teratogens, and it is imperative that their use is carefully controlled in females. The European Medicines Agency has introduced a specific pregnancy prevention programme to reduce the risk of pregnancy associated with isotretinoin (see below). Routine monitoring is also required to detect other adverse effects of oral retinoids including hepatitis and hyperlipidaemia (Table 3).

### Biologics

The pro-inflammatory cytokine, tumour necrosis factor  $\alpha$  (TNF $\alpha$ ), plays a central role in the pathogenesis of psoriasis and psoriatic arthritis. Anti-TNF $\alpha$  therapy is now an established, evidence-based treatment for severe disease. There are currently three approved agents for psoriasis: infliximab is a chimeric human and mouse monoclonal anti-TNF antibody, adalimumab is a fully humanized monoclonal anti-TNF antibody, and etanercept is a genetically engineered fusion protein of IgG1 Fc domain and extracellular portions of the human TNF receptor. Reactivation of tuberculosis is a major concern with all TNF antagonists and patients must be carefully screened before therapy. The risk may be higher with monoclonal antibodies compared with etanercept. The clinical presentation of infection is often atypical, so a high index of suspicion is required throughout treatment.<sup>11</sup> Other opportunistic infections have been reported in patients receiving anti-TNF therapy, and there is a possible small increased risk of demyelinating disease.

Ustekinumab is a fully humanized monoclonal antibody that inhibits interleukin (IL)-12 and IL-23 by binding to their p40 subunits and preventing binding to receptor proteins on the surface of immune cells. IL-12 activates CD4 and natural killer cells to induce expression of TH1 cytokines (including TNF $\alpha$ )

### Isotretinoin pregnancy prevention programme

Requirements for all female patients of reproductive age:

- Careful counselling with written information on birth deformities
- Ensure effective contraception if sexually active
- Start contraception 1 month before treatment; continue during treatment and for at least 1 month after treatment
- Negative pregnancy test before treatment, at monthly intervals and 5 weeks after completing treatment
- Start treatment on the second day of menses
- Prescription limited to a month's supply and valid for 1 week

**Table 3**



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whilst IL-23 stimulates production and survival of TH-17 cells that are thought to play a key role in the pathogenesis of psoriasis. Ustekinumab is effective in the treatment of severe psoriasis, which is its only licensed indication.

As the long-term risks of biologic therapies are not clear, NICE guidelines currently restrict their use to severe psoriasis where conventional systemic treatment has failed or is contraindicated. Eligibility criteria include a Psoriasis Area and Severity Index (PASI) of  $\geq 10$  ( $\geq 15$  for infliximab) and a Dermatology Life Quality Index score of  $> 10$  (range 0–30).

### Metastatic melanoma and inoperable basal cell carcinoma

Advances in the management of advanced skin cancer include targeted vemurafenib, an oral tyrosine kinase inhibitor of the oncogene BRAFV600 protein kinase. It is indicated for use in adults with unresectable or metastatic melanoma bearing specific tumour mutations and has been shown to improve survival compared with conventional chemotherapy. Ipilimumab, a fully human antibody that binds to cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), which is a molecule expressed on T-cells that plays a critical role in regulating natural immune responses, has also been approved for treatment of advanced (unresectable or metastatic) melanoma in adults. Vismodegib is the first agent in a new class of drugs that target the hedgehog signalling pathway and has been approved for the treatment of inoperable advanced basal cell carcinoma. It is also undergoing clinical trials in other forms of advanced cancer. ♦

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# Dermatological history and examination

Shalini Narayan

## Abstract

Skin disease is very prevalent, and according to the British Skin Foundation there are currently 8 million people in the UK affected by skin disease. The skin has a major protective and important social function, and relatively minor skin complaints can cause much anguish. Most skin diseases are not life threatening, but many are associated with a high morbidity, in the form of discomfort, disfigurement, embarrassment, social stigmatisation, and loss of work and earnings. The impact of skin disease must not be underestimated, and the Dermatology Life Quality Index (DLQI) assessment tool has been developed to assess this formally. This article will focus on how to take a comprehensive dermatological history and examination. It will also discuss diagnostic methods and tools commonly used by dermatologists, and will discuss the DLQI system.

**Keywords** dermatology; examination; hair; history; investigation; morphology; nails; skin; skin disease

In primary care, up to one-quarter of visits involve skin disorders.<sup>1</sup> Most patients can be treated in primary care, and it is therefore important that primary care physicians have a working knowledge of how to manage common skin conditions and recognize those needing referral to specialist services due to diagnostic difficulties or disease severity.

## History

History-taking from a patient with skin disease should follow a systematic and logical framework. Important points to remember include the following.

**How long have any skin lesions been present?** – ask the patient when the very first rash arose, as well as how long their current rash may have been present. Some eruptions begin acutely (e.g. drug eruptions); others are more insidious (e.g. eczema, pityriasis versicolor). The time course of individual lesions is important; urticarial lesions typically come and go within 24 hours leaving no marks behind, whereas psoriatic plaques typically change over weeks to months.

**Where did the first skin lesions arise?** – the location of certain rashes often gives clues to the diagnosis. For example, the extensor surfaces are typical for psoriasis, the flexor surfaces for atopic eczema and the toe-webs for tinea pedis.

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**Are there any symptoms?** – for example, does it itch or cause pain? Some skin conditions (e.g. scabies, eczema) can be extremely itchy, whilst others (e.g. herpes zoster) are painful. Some skin conditions cause burning (e.g. erythropoietic protoporphyria).

**Oral and topical medications** – the history of topical treatments used and the response to them is important. Topical treatments can also be the cause of rashes such as allergic contact dermatitis and photo-allergic reactions. Ask which medication was being taken at the time of onset of the rash. Possible drug-related rashes are a common reason for requesting a dermatological opinion in medical inpatients. Make a comprehensive list of medications the patient is currently taking and any recent changes, particularly in the 2–3 weeks before the rash began. Many individuals use alternative therapies such as homoeopathic and herbal remedies, but may not offer this information in a ‘conventional’ medical setting. Specific questions may be needed about such therapies, and about over-the-counter medications.

**General medical history** – it is important to be aware of a wide range of systemic conditions that can manifest as skin conditions. Examples are listed in Table 1 and Figure 1.

**Occupational and recreational history** – occupational dermatoses are common and are a frequent cause of time lost from work. Allergic contact dermatitis is more common in certain occupations (Table 2). Evidence suggesting occupational dermatosis includes:

- similar dermatoses in others at the patient’s workplace
- time relationship between exposure and dermatitis
- improvement of the rash when the patient is away from the workplace.

It is also important to ask about hobbies, recreation and sporting activities. These may also lead to contact allergies, but the patient may not associate them with their condition.

**Family history** – some skin conditions have a genetic basis; examples include atopic eczema, psoriasis, ichthyosis and keratoderma.

**Contact history** – certain skin conditions (e.g. impetigo, scabies) are acquired from others. A history of family and social contacts, including affected children at school, is important to avoid ongoing cross-infection.

**Current residence** – this is important with infectious outbreaks (e.g. scabies).

**Provocative factors** – some skin rashes develop only after exposure to ultraviolet radiation, or are exacerbated by it. Chronic actinic dermatitis is an eczematous eruption occurring on sun-exposed sites during the summer. It may be confused with atopic eczema. Discoid lupus erythematosus may be exacerbated by light exposure. Psoriasis often improves in the summer.

Always ask about other possible exacerbating factors, such as heat, cold, exercise and menses.

**Travel** – ask about overseas travel. Knowledge of diseases endemic in other parts of the world is important.

**Cutaneous manifestations of some systemic conditions**

**Diabetes mellitus**

- Granuloma annulare
- Necrobiosis lipoidica (Figure 1)
- Xanthoma
- Bullous disease
- Diabetic dermopathy
- Diabetic stiff skin
- Neuropathic leg ulceration
- Increased risk of cutaneous infection (e.g. candidiasis)

**Sarcoidosis**

- Lupus pernio of the nose
- Erythema nodosum
- Granulomatous invasion of old scars
- Cutaneous sarcoid can present in a very wide variety of ways

**Internal malignancy**

- Paraneoplastic pemphigus (solid organ cancer)
- Dermatomyositis (lung cancer, breast cancer, upper gastrointestinal tract cancer)
- Erythema gyratum repens (lung, uterus, breast cancer)
- Acanthosis nigricans

**Porphyria cutanea tarda**

- Vesicles, blisters, erosions in light-exposed areas
- Skin fragility
- Hypertrichosis
- Scarring

**Hyperthyroidism/Graves' disease**

- Pretibial myxoedema
- Thyroid acropachy (from periosteal new bone)
- Diffuse alopecia
- Palmar erythema

**Addison's disease**

- Hyperpigmentation of skin and mucous membranes caused by pituitary melanocyte-stimulating hormone and adrenocorticotropin

**Cushing's syndrome**

- Thinning of the skin, spontaneous bruising, striae, diffuse alopecia, acne and hirsutism

**Acromegaly**

- Acne
- Skin thickening

**Table 1**

**Changes in pigmented skin lesions** – patients presenting with changes in a pigmented lesion should be asked about their lifelong history of sun exposure, whether they are prone to burning on sun exposure, and any family history of multiple pigmented lesions (dysplastic naevus syndrome) or skin cancer. When assessing a pigmented lesion, it is important to ask about:<sup>2</sup>

- changes in shape
- increase in size
- changes of colour (has the lesion become darker, or has more than one colour developed within it?)
- changes in outline (from regular to irregular)
- has the lesion become more raised from the skin?
- any new symptoms (e.g. itching, bleeding).



**Figure 1** Necrobiosis lipoidica of the shins associated with diabetes mellitus.

**Examination**

Thorough examination in natural light is important. Whilst the affected area will need close examination, examine the entire skin surface. Patients presenting with a single malignancy on the face may have another on their back of which they are unaware.

Pattern recognition is also important. Full examination should include the mucosae, scalp and nails. Some rashes have a typical distribution and morphology. Palpation of rashes and individual lesions gives information about temperature, consistency, texture, surface features and tenderness.<sup>3</sup>

**General examination**

**Distribution:** Figure 2 shows the typical distribution of some common skin conditions:

- flexor – typical of atopic eczema
- extensor – typical of psoriasis
- scalp, eyebrows, sides of nose, central chest (especially in men) – typical of seborrhoeic dermatitis

**Common occupational causes of contact dermatitis**

- Hairdressers – irritant hand dermatitis, contact allergic dermatitis to para-phenylenediamine in permanent hair dye
- Brick layers – contact allergic dermatitis to chromate in cement
- Mechanics – irritant hand dermatitis to solvents, lubricants, cooling system fluid, battery acid
- Dairy farmers – milkers' nodule (paravaccinia virus)
- Gardeners – contact allergic dermatitis to plants (*Primula obconica*, Compositae), pesticides, lichens

**Table 2**

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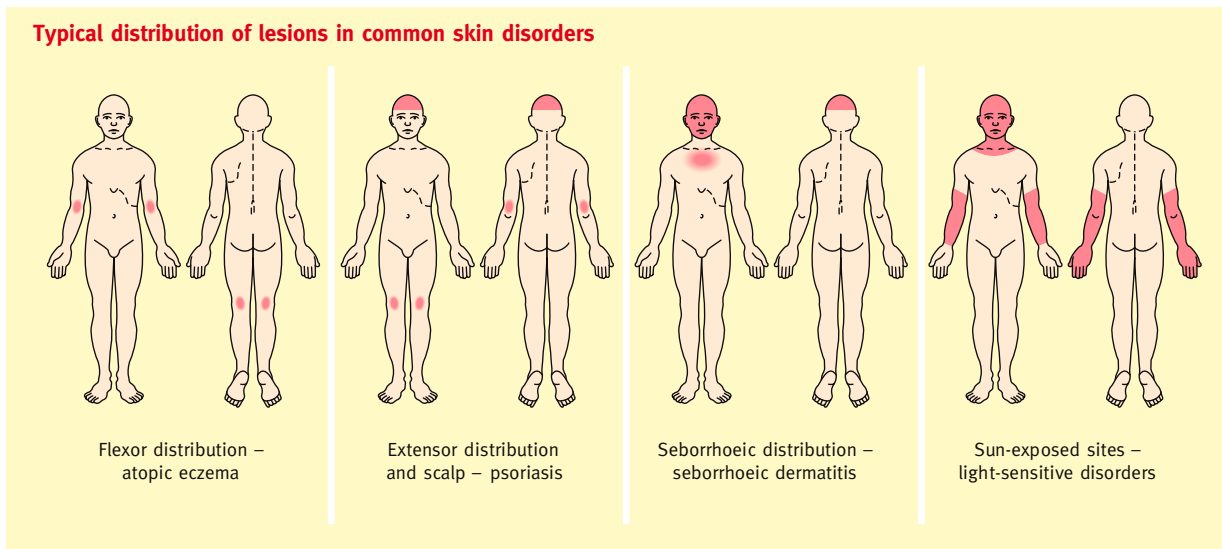


Figure 2

- sun-exposed sites – sparing of skin under the chin, behind the ears and around the scalp margin can help to differentiate photodermatoses from contact dermatitis for airborne allergens. Photodermatoses include chronic actinic dermatitis, solar urticaria, and photo-allergic rashes with systemic medication.

**Morphology:** many rashes have characteristic morphological features. Precise description of skin conditions is impossible without use of the correct terminology (Figure 3).

Full general examination is often needed. Many dermatoses are associated with systemic disease. For patients with skin tumours, examination for metastases is important.

#### Specific examination

**Hair:** there are many disorders of hair and hair growth. Some occur in isolation; others occur in association with generalized skin diseases or systemic disease.

**Alopecia** (loss of hair) can have many causes and patterns. It may be localized or generalized.

##### Localized alopecia

- Alopecia areata presents with a non-inflamed scalp, and pathognomonic 'exclamation-mark' hairs may be seen at the edges of the affected area
- Scalp ringworm (kerion) presents with inflammation and, sometimes, pustulation of the scalp
- Traction alopecia usually results from hair styling
- Trichotillomania (habitual hair-pulling) presents with a well-defined area of hair loss with broken hairs
- Lichen planus causes scarring alopecia
- Systemic lupus erythematosus causes scarring alopecia
- Aplasia cutis presents at birth and causes scarring alopecia

##### Generalized alopecia

- Androgenic alopecia tends to be diffuse, particularly over the crown

- Telogen effluvium occurs when hairs simultaneously enter the telogen (resting) phase. Hair shedding tends to occur several months after childbirth, or after severe illness
- Endocrine causes include hypothyroidism, hyperthyroidism and hypopituitarism
- Alopecia may be caused by iron deficiency or malnutrition
- Oral contraceptives and anti-mitotic drugs can cause hair loss

**Hirsutism** is excessive hair growth in women in a distribution usually seen in men, though familial and racial variations in hair growth must be taken into account. Causes of hirsutism include:

- ovarian – polycystic ovary syndrome
- adrenal – Cushing's syndrome
- virilizing tumours
- pituitary – hyperprolactinoma, acromegaly
- drug-induced – anabolic steroids.

**Inherited hair disorders** – diagnosis of disorders of hair growth may require plucked-hair analysis. Electron microscopy is performed for identification of shaft defects. There is no treatment for such disorders. Examples include:

- monilethrix – beaded hair shaft causes easy breakage
- pili torti – fragile hair because of flattened, twisted hair shaft
- trichorrhexis nodosa – node formation occurs along the hair shaft and predisposes to easy fracture.

**Hypertrichosis** – generalized excessive hair growth is uncommon. Causes include:

- anorexia nervosa
- drug-induced – minoxidil, diazoxide
- porphyria cutanea tarda
- fetal alcohol syndrome
- hypertrichosis lanuginosa – fetal lanugo hair not lost before birth

**Nails:** nail changes can provide valuable clues to associated medical and skin disorders (Table 3, Figure 4).



**Morphology of skin conditions**

| Lesion                     | Description  | Examples  |
|----------------------------|--|---|
| <b>Macule</b>              | Flat lesion, altered in colour or consistency  | <i>Cafe-au-lait</i> macules, post-inflammatory pigmentation                 |
| <b>Papule</b>              | Raised lesion < 5 mm diameter  | Molluscum contagiosum   |
| <b>Nodule</b>              | Raised lesion > 1 cm diameter  | Basal cell carcinoma  |
| <b>Plaque</b>              | Flat, elevated lesion on skin  | Psoriasis   |
| <b>Pustule</b>             | Raised lesion containing purulent material   | Sterile pustules in pustular psoriasis, infective pustules                  |
| <b>Vesicles and bullae</b> | Raised fluid-containing lesions; a bulla is larger than a vesicle  | Vesicles – chickenpox, herpes simplex type 1<br>Bullae – bullous pemphigoid |
| <b>Wheals</b>              | Transient, pruritic, raised lesions caused by local dermal oedema  | Urticaria   |
| <b>Excoriation</b>         | Partial or complete loss of epidermis caused by scratching   |   |
| <b>Annular</b>             | Ring-shaped lesions  | Granuloma annulare, erythema annulare centrifugum                           |
| <b>Lichenification</b>     | Thickening of skin with exaggerated skin markings, often from prolonged rubbing or scratching                    | Eczema  |
| <b>Atrophy</b>             | Thinning of skin giving a translucent appearance; may lose normal surface markings; blood vessels may be visible |   |



**Figure 3**

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### Nail changes associated with skin disease

- Psoriasis – pitting, ridging, onycholysis, nail loss
- Atopic eczema – pitting, transverse ridging
- Alopecia areata – fine pitting may occur in severe cases
- Lichen planus – longitudinal ridging, thinning of nail plate
- Darier's disease – notching of free edge of nail

**Table 3**

#### Diagnostic tools and methods

Most dermatological diagnoses are made clinically. Certain diagnostic tools are used to aid or confirm diagnoses as outlined below.

**Skin biopsy:** the type and depth of the lesion will dictate the type of biopsy taken (e.g. shave biopsy, punch biopsy, and incisional or excisional biopsy).

**Histological examination of fixed tissue (haematoxylin and eosin (H&E) and other stains)** – tissue is submitted in formalin and examined using H&E staining. More complex stains are often needed. Close collaboration between the dermatologist and histopathologist is needed for complex cases.

**Direct immunofluorescence (DIF)** is a technique used on skin to look for the presence and staining pattern of immunoglobulins (IgG, IgM, IgA), third component of complement (C3), or fibrinogen. One would expect DIF to be positive in diseases such as immunobullous disorders and lupus erythematosus.

**Mycological testing:** skin scrapings, hair and nail samples are taken to confirm dermatophyte infection (ringworm, tinea). Scrapings can be sent to the laboratory for microscopic examination and for culture. Potassium hydroxide (KOH) can be added

to a scraping placed on a glass slide, heated gently and examined directly under a microscope for fungal hyphae.

**Skin swabs:** swabs can be taken from vesicles, pustules, erosions and ulcers to identify bacterial or viral infection using culture technique. Skin biopsy is sometimes needed for microbiological examination for diseases such as atypical tuberculosis.

**Wood's light:** this is a low energy ultraviolet light source shone directly onto a patient's skin to detect fluorescent conditions and locate the borders of some lesions. Normal skin does not fluoresce. Certain bacterial and fungal infections will fluoresce. This light source can also be used in other conditions as shown below:

- bright white – vitiligo
- ash leaf spot – tuberous sclerosis
- coral red – erythrasma due to *Corynebacterium minutissimum*
- golden yellow – pityriasis versicolor due to *Malassezia furfur*
- green – scalp ringworm due to *Microsporum* spp.
- pink – porphyrins in urine.

**Patch testing and skin prick testing:** patch testing is used to diagnose Type 4 hypersensitivity reactions (i.e. contact allergic dermatitis secondary to direct contact with a given substance).

Skin prick testing can be used to diagnose latex allergy.

**Dermatoscopy:** the dermatoscope is a hand-held device using non-polarized light and affording  $\times 10$  magnification of cutaneous lesions. It is used mainly to identify typical features within melanocytic lesions<sup>4,5</sup> (Figures 5 and 6), but can also help to distinguish vascular lesions.

**Dermatology Life Quality Index (DLQI):** there are many ways in which skin disease can adversely affect the quality of an



**Figure 4** Nail psoriasis with pitting, ridging and onycholysis



**Figure 5** Malignant melanoma.



**Figure 6** Dermatoscopic view of malignant melanoma from Figure 5, showing blue-grey veil centrally.

individual's life. Measurement of this impact is required for clinical and health service research, but is also valuable in clinical practice in the evaluation of effectiveness of new treatments. The DLQI was developed at the Department of Dermatology, University of Cardiff.<sup>6</sup> It is a validated, reliable and reproducible questionnaire concerning adult patients' perception of the impact of their skin disease on themselves and their lives. The questionnaire can be downloaded at [www.dermatology.org.uk](http://www.dermatology.org.uk).

There are also disease-specific quality-of-life measures, including the Psoriasis Disability Index<sup>7</sup> (PDI), and the Acne Disability Index<sup>8,9</sup> (ADI); and there is also the Children's

Dermatology Life Quality Index<sup>10</sup> (CDLQI) for measurement in children. ◆

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# Dermatological pharmacology: topical agents

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## Abstract

Topical therapies constitute an important aspect of dermatological treatments. This article covers the principles of topical treatments, vehicles used and a number of commonly used topical agents, including corticosteroids. Indications for use and common adverse effects of these topical agents are mentioned.

**Keywords** calcineurin inhibitors; corticosteroids; creams; ointments; retinoids; topical treatments; vitamin D analogues

## Principles of topical therapy

Topical therapy allows direct delivery of drug to the skin with minimal risk of systemic adverse effects. Problems include poor compliance because of difficulty using the drug and inconvenience of applications. The effectiveness of topical drugs depends on their ability to penetrate the epidermis. This is influenced by the choice and concentration of drug, its vehicle or base, and the age and degree of hydration of the skin.

- Substances enter aged skin more easily, but clearance into the circulation is slower because of changes in the dermal matrix and reduced vasculature, so the skin may be more susceptible to both beneficial and adverse effects of topical medication.
- Use of emollients to increase skin hydration before application of topical agents such as corticosteroids may increase their penetration fivefold. Occlusion of the skin will also increase drug penetration.
- The specific condition and body site to be treated is also important; for example, absorption is greater at flexural sites and less potent corticosteroids are therefore required.

## Vehicles

An understanding of the available vehicles is important for effective prescribing of topical therapies. Vehicles hydrate the skin, can have an anti-inflammatory effect and help the active drug penetrate the skin.

- Creams are water-based products with a cooling and emollient effect. They contain preservatives to prevent bacterial and fungal growth, but the preservatives may

## What's new?

- The calcineurin inhibitors tacrolimus and pimecrolimus are licensed treatments for atopic eczema
- Tacrolimus is now licensed for maintenance therapy of atopic dermatitis for the prevention of flares and the prolongation of flare-free intervals, Topical vitamin D analogues such as calcitriol can be used for facial and flexural psoriasis
- UK National Institute for Health and Clinical Excellence (NICE) guidelines for the treatment of atopic eczema have been published, which include topical corticosteroids<sup>3</sup>
- Retapamulin 1% ointment is a new antibacterial licensed for treatment of impetigo, infected lacerations and sutured wounds

lead to sensitization and allergic contact dermatitis. Creams are less greasy than ointments and are cosmetically better tolerated.

- Ointments contain no water; they are oil-based products providing an occlusive layer over the skin surface that helps to retain water. This hydrates dry and scaly skin and enhances absorption, and ointments are therefore useful in chronic dry conditions. They contain no preservatives.
- Lotions are watery suspensions that can be used over hairy and large body surface areas. They have a drying, cooling effect.
- Gels are watery suspensions of insoluble drugs such as corticosteroids, salicylic acid and retinoids. Gelling agents are added to aid their absorption.

## Topical agents

A list of common topical agents is shown in [Table 1](#).

## Emollients

The term 'emollient' covers a diverse range of products, including soap substitutes, bath additives, creams, ointments and even aerosol spray products. They are important in the management of itchy, dry skin conditions, giving symptomatic relief, and may reduce requirements for topical corticosteroids. Their effects are temporary and frequent applications are needed even after initial clinical improvement. Choice of emollient is guided by the nature of the condition, its severity and patient preference. Emollient creams, ointments and sprays are best applied following a bath or shower. Many emollients contain preservatives and other additives, and sensitization may rarely occur.

## Topical corticosteroids

Topical corticosteroids are classified according to their potency ([Table 2](#)). The cutaneous effects of topical corticosteroids include vasoconstriction, reduced dermal blood vessel permeability and inhibition of phospholipases, fibrin and kinins. In addition, inhibition of phospholipases causes blockage of the arachidonic acid pathway, which leads to a cascade of inflammatory mediators. Anti-inflammatory effects thus occur, and corticosteroid-responsive conditions such as eczema usually exhibit clinical

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**Topical agents**

| Agent                  | Indications                  | Side effects   |
|------------------------|------------------------------|--|
| Corticosteroids        | Inflammatory dermatoses      | Striae, telangiectasiae, bruising, allergic contact dermatitis, depigmentation, worsening of infection, rebound phenomenon, suppression of hypothalamic–pituitary–adrenal axis |
| Emollients             | Xerosis, eczema, psoriasis   | Folliculitis   |
| Retinoids              | Psoriasis, acne, photodamage | Skin irritation, erythema  |
| Vitamin D analogues    | Plaque psoriasis             | Skin irritation, pruritus, erythema, hypercalcaemia  |
| Coal tar               | Plaque psoriasis             | Skin irritation, staining, folliculitis, skin cancers  |
| Dithranol              | Plaque psoriasis             | Skin irritation, staining  |
| Calcineurin inhibitors | Atopic eczema                | Skin irritation, burning, erythema, infections, alcohol intolerance  |

**Table 1**

improvement within 2 weeks of starting treatment with a potent agent. Inflammatory skin conditions involving delicate skin on the face, flexures or genitalia require a mild or, at most, moderately potent corticosteroid. In contrast, palms, soles and markedly thickened skin (as may occur with chronic scratching) often require a potent or very potent agent.

Corticosteroids should be applied once or twice daily. The quantity applied can be assessed using the ‘fingertip unit’ (FTU) concept – an amount of ointment or cream the length of an adult fingertip is about 0.5 g and is sufficient to treat 300 cm<sup>2</sup> of affected skin (Figure 1).<sup>1</sup> A single application for one arm or leg, for example, requires 3 FTU or 6 FTU, respectively.

Failure to respond to topical corticosteroids may occur as a result of incorrect diagnosis, skin infection or infestation, contact allergy, poor compliance or inadequate application of treatment. Under-treatment through use of too weak or inadequate amounts of topical corticosteroids is a significant problem; it is now seen more often in clinical practice than over-treatment through long-term use of potent agents. The risk of adverse effects increases with corticosteroid potency.

**Topical retinoids**

The topical retinoids belong to a unique group of drugs that are widely prescribed for skin conditions, including psoriasis, acne and photodamage. The first topical retinoids were synthetic derivatives of vitamin A. Newer compounds (e.g. adapalene) have different structural configurations, but also act via nuclear retinoid receptors. Adverse effects of topical retinoids include skin desquamation and erythema, producing mild irritant dermatitis.

**Topical corticosteroids**

| Potency     | Corticosteroid  | Risk of skin thinning with long-term use |
|-------------|---|--|
| Mild        | Hydrocortisone  | Low                                      |
| Moderate    | Clobetasone butyrate                                  | Some                                     |
| Potent      | • Betamethasone valerate<br>• Hydrocortisone butyrate | High                                     |
| Very potent | Clobetasol propionate                                 | Very high                                |

**Table 2**

**Tazarotene** is a selective retinoid receptor agonist with anti-inflammatory and antiproliferative effects on keratinocytes. It is used for plaque psoriasis affecting up to 10% of the skin area.<sup>2</sup> It is applied once daily for up to 12 weeks and is available as a 0.05–0.1% gel. Adverse effects include local skin irritation, erythema, burning, photosensitivity and worsening of psoriasis. Tazarotene should be avoided in women of childbearing age, and on facial and flexural skin. Combination treatment with topical corticosteroids and phototherapy is effective.

**Adapalene** is a topical retinoid drug used for acne. It is less of an irritant than other, older retinoids and is effective in both comedonal and inflammatory acne.

**Tretinoin and isotretinoin** are useful in comedonal acne, but have little effect on inflammatory acne.

**Topical vitamin D derivatives**

Vitamin D analogues have become established as the first-choice topical therapies in the treatment of psoriasis. These products are cosmetically acceptable because they are odourless and do not stain or mark clothing or skin – a significant advantage over



**Figure 1** Demonstration of 1 fingertip unit (FTU).

traditional topical treatments such as coal tar and dithranol products. Topical vitamin D derivatives can be combined with topical corticosteroids and phototherapy.

**Calcipotriol** is a vitamin D analogue that suppresses keratinocyte proliferation and induces epidermal differentiation. It is used in the treatment of mild-to-moderate plaque psoriasis affecting up to 40% of the body surface area. It should not be used in erythrodermic or pustular psoriasis. Maximal benefits are seen after 8–12 weeks of once-daily or twice-daily application. Hypercalcaemia may occur if the maximum recommended dose of 100 g per week is exceeded. Other adverse effects include local irritation, pruritus and erythema. Calcipotriol is contraindicated in pregnancy and should not be used on the face.

**Tacalcitol** is used once daily, preferably at night. Its adverse effects are similar to calcipotriol. It is not licensed for use in children.

**Calcitriol** is the newest topical vitamin D analogue. It is licensed for use on the face and flexures in addition to psoriasis on the trunk and limbs. It is applied twice daily up to a maximum of 210 g per week.

#### Calcineurin inhibitors

Calcineurin inhibitors belong to a new class of topical immunomodulators that act by reducing inflammation via T-cell suppression. Tacrolimus and pimecrolimus have been appraised by the UK National Institute for Health and Clinical Excellence (NICE).<sup>3</sup> They are recommended as second-line treatment for moderate-to-severe atopic eczema not controlled by topical corticosteroids or when there is a high risk of adverse effects such as skin atrophy. The main adverse effects are skin irritation, burning, erythema, infections and alcohol intolerance. Long-term effects such as predisposition to skin malignancy are unknown. A safety review by the European Medicines Evaluation Agency (EMA) has recommended caution with use in order to reduce potential risks of skin cancer and lymphoma as far as possible. These treatments should be started only by physicians (including GPs) with a special interest and experience in dermatology.

**Tacrolimus** is used on all areas of the body, including the face and flexures. In adults, 0.1% ointment can be used twice daily for 3 weeks initially; 0.03% is then used once or twice daily. In children over the age of 2 years, 0.03% ointment only is licensed. Tacrolimus (0.03% and 0.1%) is now licensed for maintenance therapy (twice weekly) of moderate-to-severe atopic dermatitis for the prevention of flares and the prolongation of flare-free intervals especially in patients with frequent flares (e.g. four or more flares per year). This maintenance therapy is for patients

with an initial response after 6 weeks of twice-daily therapy with clear or almost clear skin.<sup>4,5</sup>

**Pimecrolimus** is available as a 1% cream and can be used twice daily on sites including the face, neck and flexures in adults and children aged 2–16 years. It can be used short term or as intermittent long-term treatment to prevent flares. The adverse effects are similar to those of tacrolimus.

#### New antibacterials

**Retapamulin** is a derivative of the antibacterial pleuromutilin, a product of *Pleurotus mutilus*, an edible mushroom. This 1% ointment is a new antibacterial licensed for treatment of impetigo, infected lacerations and sutured wounds for patients aged 9 months or above. It should be used on the infected area twice daily for 5 days. Adverse effects include skin irritation, pain, itching and redness.

#### Topical therapy in the elderly

Use of topical therapies in the elderly has increased challenges, especially with the practical aspects. Those with co-morbidities (e.g. poor vision, arthritis) or those living alone may require assistance to apply topical treatments. Carers, friends and family may need to be involved and educated about applying the treatments. Instructions should be simple, clear and in writing, specifying amounts and duration of specific treatments. The site of application of treatments such as topical corticosteroids and vitamin D analogues should be clear to avoid inadvertent use on the wrong site (e.g. potent corticosteroid applied to the face). Day-care treatment and education can be very helpful for the patient and carers. A short stay in hospital can often 'turn the corner' in the topical management of the elderly with skin disease especially if there are difficulties with mobility and travel. ♦

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