A review on drug induced skin disorders: pathophysiology and therapeutics

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ABSTRACT

Drugs are the central part of treatment of various disorders. The consequence of drug use may be either positive outcomes (clinical effect of the drug) or negative outcomes (adverse drug events). That is, it contains both risk and benefit. In recent years multiple disorders treated with many drugs by monotherapy or by fixed-dose therapy existing in the market which leads to increased drug-related problems one among that is drug-induced disorders. Morbidity and mortality have increased due to drug-induced disorders. This study was aimed to describe the various drugs induces skin disorders, its pathophysiology, diagnosis and treatment approach. We completed a review of the current evidence for various drug-induced skin disorders its causative drugs and therapeutic intervention of drug-induced skin disorders. A review through Medline, Embase, Pubmed, Wiley online library and selected studies related to drug-induced skin disorders. This is the comprehensive review of drug-induced skin disorders, designed to address prospectively its etiopathogenesis and clinical management. Penicillin, sulfa, phenylbutazone, Tetracycline are the most common drug induces various skin disorders. There is not much significant differences in the clinical, histopathological or immuno-pathological features between various skin disorders and drug induced skin disorders. Hence knowing the etiopathology, and differential diagnosis is important to a proper treatment approach.

Keywords: Drug-induced disorders, Risk-benefit, Fixed dose therapy, Skin disorders

INTRODUCTION

The responsible provision of drug therapy to achieve a definite therapeutic outcome that improves the patient’s quality of life. The problems may be related to patient’s current drug therapy, drug administration, drug compliance, drug toxicity, adverse drug reactions and failure to achieve desired outcomes by the treatment.\(^1\)

Adverse drug reaction is that all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. A response to a drug which is noxious and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or modification of physiological function.\(^2\)

This contributes to overall health care costs by increasing morbidity and even mortality rate and it affects the patient's confidence in the prescriber and future adherence with medication. The most common allergic drug reactions are dermatologic.

Skin is an important administration route of drugs for both topical and systemic therapy. A skin is of particular importance when adverse effects of drugs are considered. Almost any type of skin eruption can be secondary to medication. Drug-induced skin disease is one of the commonest dermatological presentations in both
hospitalized and ambulatory patients. It affects 2-3% of hospitalized patients, and it is estimated that 1 in 1000 hospitalized patients have a serious cutaneous drug reaction.3

SKIN STRUCTURE AND FUNCTION

The skin is the largest organ of the body, is divided into three (main) distinct layers, the epidermis, the dermis, and the hypodermis (subcutaneous tissue) as the epidermis is nonvascular and consists of stratified squamous epithelial cells that are of two distinct types, keratinocytes, and dendritic cells. The epidermis consists of five distinct layers, beginning with the innermost:

• Stratum germinativum (basal)
• Stratum spinosum (prickle)
• Stratum granulosum (granular)
• Stratum lucidum (lucid)
• Stratum corneum (horny)

The dermis consists of connective tissue, cellular elements, and ground substance with rich blood and nerve supply. The sebaceous glands and shorter hair follicles originate in the dermis that can be divided into two distinct sub-layers, the papillary and reticular units. The papillary layer is adjacent to the epidermis and has a rich supply of blood vessels. The reticular sub-layer contains coarser tissue that connects the dermis and subcutaneous tissue (hypodermis). The connective tissue provides support and elasticity of the skin. During itching, the cellular elements include fibroblasts, histiocytes, and mast cells are increased. Poly-morphonuclear leukocytes and eosinophils, members of the myeloid group, are seen in dermatoses. Lymphocytes from the lymphoid group are common in inflammatory lesions of the skin.

The hypodermis is composed of loose connective tissue. It contains a unit for the formation and storage of fat which regulates body temperature, acts as a food reserve, and cushioning. The hypodermis also supports the blood vessels and nerves that pass from tissues beneath to the dermis. Deeper hair follicles and sweat glands originate in the hypodermis.

The skin prevents harm from external agents like ultraviolet radiation, pathogenic organisms, and chemicals. Various factors can alter the effectiveness of the barrier including age, underlying disease states, use of medications (topical or systemic), and the integrity of the stratum corneum. Other skin functions involve sensation, temperature control, development of pigment, synthesis of some vitamins, and moisture regulation.4,6

Histopathologic inflammation and neoplastic patterns are the cutaneous reactions caused due to drugs. Drug-induced skin reactions consist of a wide variety of rashes that depend on the route of administration (e.g., contact versus systemic) as well as a type of cutaneous response and molecular mechanism underlying the reaction. An intravenous (IV) immunologic reaction (delayed hypersensitivity) manifests as contact dermatitis and commonly elicited route of reaction. The drugs such as antihistamines, antibiotic ointments, local anesthetics, and paraben esters in cosmetic creams and lotions are the common cause of immunologic reaction. Non-specific pruritus or maculopapular eruptions are the common cutaneous drug reactions during systemic administration and the adverse drug reactions (ADRs) are the major health concern among them.7,8

Other types of derma reactions include acute urticarial angioedema. Erythema multiforme (bullous and non-bullous), Stevens-Johnson syndrome (SJS), urticaria in association with serum sickness-like reactions, and urticaria associated with anaphylactic reactions. Photo-allergic reactions to an antigen formed by interaction of the drug with light and binding of the altered drug to a cutaneous protein to form a complete antigen.9

Drug reactions causing changes to skin function and some drugs alter the ability of the skin and associated structures (hair and nails) to perform their function normally.

DRUGS CAUSING LIGHT-INDUCED ERUPTIONS

Topical preparations

Topical non-steroidal anti-inflammatory drugs (NSAIDs), Components of sunscreen such as para-aminobenzoic acid (PABA), benzophenone,

Systemic drugs

Phototoxic reactions amiodarone, nalidixic acid, NSAIDs, chlorpromazine, tetracyclines, photoallergic reactions, griseofulvin, NSAIDs, sulphonamides, sulphonylureas, thiazide diuretics,10

Drug-induced photosensitivity reactions are divided into photo-toxicity (non-immunologic). For diagnosis photo testing and photo patch testing can be done. Initially, the management is prevention, intervening patients regarding the possibility of increased sun sensitivity and the use of sun protective measures. Once the eruption has occurred, it may be necessary to discontinue that medication and treat the eruption with a potent topical corticosteroid.3,11,12

DRUGS CAUSING SKIN PIGMENTATION

Amiodarone, anticonvulsants, antimalarials, β-Blockers, imatinib, imipramine, mepacrine, methyldopa, oral contraceptives, phenothiazines, psoralens, tetracycline.10

The pathogenesis is variable according to the medication type and it can involve an accumulation of melanin, sometimes a nonspecific cutaneous inflammation, often for sun exposure, for triggering drug, and a drug synthesize
special pigments or deposition of iron damage to the dermal vessels. Diagnosis based on histological findings. With respect to dermal structures such as vessels or adnexes, the colored particles are often concentrated within dermal macrophages. Treatment is often limited to sun-avoidance, laser therapy.13,14

**DRUGS CAUSING HAIR DISORDERS**

Alopecia

Acetretin, anticoagulants, antithyroid drugs, beta-blockers, cinetidine, cytotoxic drugs, gold salts, interferons, isotretinoin, leflunomide, lithium, sodium valproate, statins, tacrolimus.

Hirsutism/hypertrichosis

Acetazolamide, anabolic steroids, androgens, corticosteroids (topical and systemic), ciclosporin, danazol, minoxidil, oral contraceptives, penicillamine, phenytoin, tamoxifen, verapamil.10

The pathogenesis involves various etiologic factors such as histamine, cutaneous sensory receptors. C-nerve fibers and cytokines. Branches of the trigeminal nerve and blood vessels present in the sensory innervation from the scalp skin which contains more hair follicles and more sebaceous glands. Skin has unmyelinated C-fibers transmit sensory (pruritus) signals via the contralateral spinothalamic tract to the multiple areas in brain that are responsible for sensation and emotion. In the mechanisms of pruritus, several mediators (histamine, tryptase, substance P, bradykinin, and opioid) play a role. Histamine-induced itch response explained by using intradermal micro dialysis on the scalp by Rukweid et al microorganisms, including Malassezia species, Propionibacterium species, and staphylococci, are commonly found on the scalp. Diagnosis for dermatologic cause (detailed history, physical examination, investigation-skin biopsy) and non-dermatologic cause [detailed history, physical examination- neuropathic cause (nerve conduction study, electromyography, magnetic resonance imaging)], systemic cause [drug history, complete blood count (CBC), blood urea nitrogen (BUN), serum creatinine, serum bilirubin, alkaline phosphatase (ALP), thyroid stimulating hormone (TSH), fasting blood glucose (FPG), anti-nuclear antibody (ANA), anti-HCV, anti-HIV, chest X-ray (CXR)], psychogenic cause- psychiatric consultation. Medication involve glucocorticoids, calcineurin inhibitors- pimecrolimus, tacrolimus, menthol, capsacin, liquor carbonic detergents, shampoos with anti-inflammatory effects, phototherapy, psychotherapy.15,16

**DRUGS CAUSING ACNE**

Androgens (in women), corticosteroids (oral and topical) and ACTH (including inhaled preparations), ciclosporin, Epidermal growth factor receptor (EGFR) antagonists (cetuximab), ethambutol, haloperidol, isoniazid, lithium, oral contraceptives, phenobarbital, phenytoin, propylthiouracil.10

In the body, drug potentially causes an abnormal cell-mediated immune response. Drug-induced acne is a condition that occurs due to certain medication or drug side effects. Acne is a common skin condition that causes inflamed red spots/lesions to appear on the face, neck, shoulders, and other regions. The condition occurs, when the tiny hair follicles become clogged with dead cells and oil. It can be treated primarily by discontinuing or the causative medication, and through the use of suitable creams and gels, dermabrasion, skin surgery, and even laser therapy. Through a simple physical examination and by collecting patients’ demographic details, family history, past and present medical and medication history, etc. If secondary infections develop, then a culture test, invasive methods (skin biopsy) may be done.

Treated by discontinuing the medication responsible for the side effect, use of antiseptic, antibiotic topical applications, anti-inflammatory gels, lotions and creams. Benzoyl peroxide is the most common ointment for milder forms of acne and topical retinoids are used for regulating the hair follicles. Topical retinoids help treat acne by removing the dead skin, from the affected region. In severe acne, isotretinoin used.

A cosmetic procedure (dermabrasion) is performed under local anesthesia, the raised lumpy acne scars and skin dark spots are abraded. The other cosmetic procedures such as chemical peeling, minor skin surgery (punch excision), and microdermabrasion may be used.

**Phototherapy**

A controlled exposure to light for a certain time duration. For long-lasting acne this method is not very effective. And avoiding foods (dairy products, sugar-rich foods, chips) that worsens or triggers the acne condition.17-22

**DRUGS CAUSING LICHENOID ERUPTIONS**

Antimalarials- chloroquine, mepacrine, aspirin, ACE inhibitors, β-blockers, calcium channel blockers (amlodipine, nifedipine), carbamazepine, ethambutol, gold salts, imatinib, interferon, lithium, methyldopa, NSAIDs, penicillamine, phenothiazines, quinine, sulphonylurea.10

Drug-induced lichen planus (lichenoid drug eruption) is an uncommon condition that occurs due to certain medication (side effect). Skin lesions on the arms, legs, and trunk, asymptomatic in some individuals, itching from lesions on the skin and pain from lesions in the mouth are the manifestations. Diagnosed by a complete physical examination, medical history, dermcopy, skin or tissue biopsy. The primary treatment for drug-induced lichen planus in symptomatic individuals is discontinuation or stoppage of the medication. For mild skin conditions,
washing with mild (antibacterial) soap and applying warm compress, may be advised. Use of topical steroidal creams and lotions, administration of systemic steroids. Oral steroids for severe itching, painful oral lesions, and pain while swallowing, and cosmetic issues, immunosuppressive therapy (cyclosporine- mouthwash for oral lesions), photo-chemotherapy- failure for medication, systemic retinoids in case of severe signs and symptoms.

**Self-care tips**

Wear smooth cotton clothes, use only mild perfumes, soaps, and detergents, drinking lots of water or fluids.23-25

**DRUGS CAUSING URTICARIA/ANGIOEDEMA**

Antibiotics (penicillin’s- parenteral route), barbiturates, ACE inhibitors, angiotensin receptor blocker, levamisole, NSAIDs, opiate analgesics, phenolphthalein, quinine, rifampicin, sulphonamides, thiopental, vancomycin.10

Drug-induced angioedema occur in response to a wide range of drugs and vaccines. A study by Ormerod et al it is seen in 0.16% of medical inpatients and accounts for 9% of chronic urticaria or angioedema seen in dermatology outpatient departments. And in Angiotensin-converting enzyme inhibitors (ACEIs) in the causation of life-threatening angioedema is never accompanied by urticaria and occurs via a kinin-dependent mechanism. Drug-induced urticaria is seen in association with anaphylaxis, angioedema, and serum sickness. Diagnosis requires a detailed history, skin testing. Treatment for mild reactions by avoidance of the causative drug and antihistamines. For anaphylactic shock, treatment with epinephrine (adrenaline), corticosteroids and antihistamines are required. Patients should be educated to inform medical staff about previous drug reactions.26-20

A difference seen between urticaria and angioedema based on its location (papillary dermal, reticular dermal, subcutaneous/submucosal), vasodilatation (+++/+-), edema (+/+), cellular infiltration (sparse perivascular infiltrates of mainly neutrophils, eosinophils, monocytes and T-lymphocytes in urticaria, little or no cellular infiltrate, except in allergic angioedema where eosinophils may be seen in angioedema), red color lesions in skin only, itch in urticaria and variable skin color lesions in skin and mucosa, pain and heat in angioedema, seen respectively.

**DRUGS CAUSING FIXED DRUG ERUPTIONS**

Ampicillin, aspirin, barbiturates, dapsone, metronidazole, NSAIDs, oral contraceptives, phenytoin, quinine, sulphonamides, tetracycline’s, certain foods such as cashews and licorice.10

Fixed drug eruption (FDE) describes that due to systemic exposure to a drug the development of one or more annular or oval erythematous patches these reactions normally resolve with hyperpigmentation and may recur at the same site with re-challenge to the drug. An antibody-dependent, cell-mediated cytotoxic response, CD8+ effector/memory T cells play an important role in reactivation of lesions with re-exposure to the offending drug (hapten), that binds to basal keratinocytes, leading to an inflammatory response. Through liberation of cytokines such as tumor necrosis factor-alpha, keratinocytes may locally up-regulate expression of the intercellular adhesion molecule-1 (ICAM1). The up-regulated ICAM1 has been shown to help T cells (CD4 and CD8) migrate to the site of an insult. Drug eruptions often have nonspecific clinical findings. Diagnosis is not always easy, the residual hyperpigmentation serves as an indicator of site recognition, as in the case non-pigmenting fixed drug eruptions, which do not have any residual hyperpigmentation. Other forms of FDE are pigmenting fixed drug eruption, generalized or multiple fixed drug eruption, linear fixed drug eruption, wandering fixed drug eruption, non-pigmenting fixed drug eruption, bullous fixed drug eruption, eczematous fixed drug eruption, urticarial fixed drug eruption, erythema dyschromicum perstans-like fixed drug eruption, vulvitis, oral, psoriasiform, cellullitis like eruption.30-34

**DRUGS WHICH EXACERBATE PSORIASIS**

ACE inhibitor, antimalarials – chloroquine, mepacrine, biological therapy targeting tumor necrosis factor alpha (TNF-alpha), beta-blockers (most frequently atenolol, oxprenolol and propranolol), corticosteroids, for example prednisolone, G-CSF (granulocyte-colony stimulating factor), lithium, NSAIDs.10

Drug-induced/exacerbate psoriasis occur in response to a wide range of drugs. “Psoriasiform drug eruption” is a heterogeneous group of disorders that clinically, histologically stimulate psoriasis at some point during the disease. According to this concept drug-induced psoriasis is an auto-immune disease of the beta receptors of the skin. The initial and central event is the alteration of the immunological properties of the receptor due to an interaction with the drug. This leads further to the activation of an immunological cascade that results in a reduction in the functional activity of the receptors and through a known pathway to the development of the clinical manifestation of the disease even in patients without a family history of psoriasis or in predisposed individuals. Morphological types can vary from plaque psoriasis to pustular psoriasis and even erythroderma. Certain established agents are known to trigger psoriasis. Many of the biological agents and targeted therapies can trigger psoriasis by activating signaling pathways. Reduction in a dosage of the drug is an additional option for treatment-resistant cases. If in the case of beta blockers induced psoriasis is present only in localized areas, emollients alone can be helpful. Exacerbation of psoriasis by beta blockers can be persistent and resistant to therapy unless they are discontinued. Treatment of erythroderma
resulting from beta-blocker therapy should be targeted at decreasing trans-epidermal fluid loss.35.36

Anti-malarial in the skin through the inhibition of transglutaminase, influence cellular proliferation in psoriasis. Patients on chloroquine and hydroxychloroquine with psoriasis is considered by some to be a contraindication. Tetracyclines provoke psoriasis through reduction of intracellular cyclic adenosine monophosphate (cAMP) and by the interaction with arachidonic acid and its metabolites. Avoid the drug in patients with clinical evidence of psoriasis and in those with a positive family history or with human leukocyte antigen (HLA)-B13, B17, and B27 genotypes.37,38

NSAIDs aggravate psoriasis by inhibiting the metabolism of arachidonic acid by the cyclo-oxygenase (COX) pathway leading to the accumulation of leukotrienes. Lithium provoked psoriasis alters in calcium homeostasis and serotonergic function due to depletion of inositol monophosphate. It can be managed with conventional treatments, such as topical corticosteroids, keratolytic, vitamin D analogues, oral retinoids, psoralen plus ultraviolet A (PUVA) therapy, and methotrexate. Hospitalization is required to monitor hypovolemia and hemodynamic instability that requires aggressive fluid resuscitation. These cases should be treated aggressively with systemic and topical agents in concordance with discontinuation.39-41

**DRUGS CAUSING ERYTHEMA MULTIFORME**

Allopurinol, antiretrovirals- neviripine, barbiturates, dimetidine, dapsone, gold salts, isoniazid, lamotrigine, leflunomide, macrolide antibiotics, mefloquine, NSAIDs, penicillin’s, phenytoin, rifampicin, sulphonamides.10

Vaccinations include Bacillus Calmette–Guérin, diphtheria - pertussis - tetanus, measles-mumps-rubella, hepatitis B, meningitis, smallpox, human papillomavirus, pneumococcal, and rabies.

Erythema multiforme (EM) is an acute, immune-mediated condition characterized by the appearance of distinctive target-like lesions on the skin. These lesions are often accompanied by erosions or bullae involving the oral, genital, and/or ocular mucosae. In response to a wide range of drugs listed it induces erythema multiforme. In clinical and histopathologic findings have led to controversy over the distinction between EM and Stevens-Johnson syndrome (SJS), an often drug-induced disorder that may present with cutaneous, targetoid lesions and mucosal erosions.42

Nivolumab and ipilimumab are monoclonal antibodies against programmed death 1 and cytotoxic T-lymphocyte associated antigen, both of which regulate excessive T-cell activation. Although these agents induce antitumor immunity against melanoma, the modified immune condition may result in an unexpected adverse reaction.43,44

**DRUGS CAUSING STEVENS-JOHNSON SYNDROME AND TOXIC EPIDERMAL NECROLYSIS**

Allopurinol, antiretroviral- nevirapine, carbamazepine, co-trimoxazole, dapsone, gold salts, lamotrigine, leflunomide, NSAIDs- meloxicam, diclofenac, penicillin’s-amoxicillin, ampicillin, phenobarbitone, phenolphthalein, phenylbutazone, phenytoin, sulphadiazine, sulphasalazine, tetracyclines.10

Stevens-Johnson syndrome (SJS), a form of mucocutaneous adverse reaction affecting <10% of body surface area is almost always drug related. Clinical squal includes complications from permanent mucocutaneous scarring in the eyes, gastrointestinal, respiratory, genitourinary tracts, psychologic distress, and polymorphic lesions such as erythematous macules, papules, plaque, vesicles, and bullae affecting distal extremities with positive Nikolsky’s sign. Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are life-threatening hypersensitivity reactions mainly caused by drugs. The disease can be classified based on body surface area (BSA) into SJS (<10% BSA), SJS- TEN overlap (10%–30% BSA) and TEN (>30% BSA).45

Management of SJS/TEN by immediate cessation of an offending drug and adequate supportive care in intensive care unit. Systemic corticosteroids, intravenous immunoglobulin therapy (IVIG), and other immunosuppressive therapy are used for its management.36-48

**OTHER DRUGS AND DRUG INDUCED SKIN DISORDERS**

With an ever-expanding list of medications, to assess the relationship between drugs and adverse reactions the adverse drug reactions probability scale can be helpful if a clinician is faced with a difficult decision in high-risk patients on multidrug regimens. The other common drug induced skin disorders are Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) the common cause drugs are allopurinol, antiretrovirals, for example efavirenz, carbamazepine, cotrimoxazole, lamotrigine, minocycline, phenobarbitone, phenytoin, sulphadiazine, sulphasalazine, vancomycin.

Drugs causing exanthematous eruptions are as follows amoxicillin, ampicillin-a, bleomycin, captopril, carbamazepine, chlorpromazine, co-trimoxazole, gold salts, nalidixic acid, NSAIDs, phenytoin, penicillin.

Drugs causing acute generalised exanthematous pustulosis are allopurinol, amoxicillin, carbamazepine, cefuroxime, co-trimoxazole, doxycycline, macrolide antibiotics, for
example, erythromycin, pristinamycin, metronidazole, lamotrigine, phenytoin, sulphasalazine, vancomycin.

Drugs causing lupus erythematosus are anticonvulsants: phenytoin, beta-Blockers, chlorpromazine, griseofulvin, hydralazine,isoniazid, lithium, methyldopa, oral contraceptives, penicillamine, phenytoin, procainamide, propylthiouracil, sulphasalazine, terbinafine.  

Although drug reactions are extremely common, and many are immunologically mediated. Some studies conducted in derma department patient has urticarial resulting from an antibiotic, penicillin and related compounds. Drug-induced cutaneous vasculitis drugs implicated include penicillin, sulfa, phenytoxbutazine, thioracil, isoniazid and busulfan. Drug induced erythema nodosum reactions suspected agents have been iodides, bromides, penicillin, salicylates, phenolphthalein (red dye), sulfa drugs, barbiturates, tetracycline, aspirin and phenytoxbutazine. Drugs induce phototoxic reactions include coal tar derivatives, systemic administration of dimethyl chlorotetracycline (dectomycin), chlorpromazine, sulfa drugs. Ampicillin induce maculopapular eruptions. Drugs commonly responsible include sulfa, penicillin, barbiturates, salicylates, anticonvulsants, phenothiazines, and phenytoxbutazine in erythema multiforme. In Herfindal et al study drugs causing urticaria/angioedema are antibiotics (penicillin’s- parenteral route), barbiturates, ACE inhibitors, angiotensin receptor blocker, levamisole, NSAIDs, opiate analgesics, phenolphthalein, quinine, rifampicin, sulphonamides, tiotepental, vancomycin. Drugs causing erythema multiforme are allopurinol; antiretrovirals- nevirapine; barbiturates, cimetidine, dapsone, gold salts, isoniazid, lamotrigine, leflunomide, macrolide antibiotics, mefloquine, NSAIDs, penicillins, phenytoin, rifampicin, sulphonamides. Drugs causing Stevens–Johnson syndrome (SJS)- allopurinol, antiretrovirals- nevirapine, carbamazepine, co-trimoxazole, dapsone, gold salts, lamotrigine, leflunomide, NSAI-Ds-meloxicam, diclofenac, penicillins- amoxicillin, ampicillin, phenobarbitone, phenolphthalein, phenytoxbutazone, phenytoin, sulphasalazine, sulphasalazine, tetracyclins. A study by Ismail et al ibuprofen, allopurinol, chloroquine, penicillamine, sulfasalazine, carbamazepine, etosuximide, phenobarbital, phenytoin, valpoic acid, amoxicillin, imipenem, ciprofloxacin, clindamycin, doxycyclin, erythromycin, sulfadiazine, sulfamethoxazole- trimethoprim, dapsone, fluconazole, nystatin, nevirapine, abacavir, efavirenz, tamoxifen, verapamil, enalapril, acetazolamide induce SJS.

CONCLUSION
Drug induced skin disorder continues to be a major health problem. Understanding the pathogenesis of drug induced various skin disorder not only helps to achieve a greater appreciation of the disease process, but it is also useful in guiding treatment methodologies, resistance can be avoided and can improve the treatment adherence. The diagnostic approach to patients is complicated and requires multidisciplinary interactions due to the complex nature of the pathogenesis and overlapping of diagnosis with other skin disorder. Although the understanding of the pathogenesis has improved significantly in recent years, it remains one of the great challenges for medical research. Further investigation and determining more effective treatment with lower adverse effects are necessary. Patients should be encouraged to avoid alcohol, excessive sun exposure, smoking, stress factors and other triggering factors that can all affect the clinical course of the disease.

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