NEWS, VIEWS, & REVIEWS

Repurposing of Drugs for Dermatologic Applications: Five Key Medications

Dermatologists and other physicians frequently prescribe medications off-label for the treatment of cutaneous disease.[1,2] Off-label prescribing refers to prescription of a drug in a way that diverges from FDA-approved use. It may represent first-line therapy, be incorporated into treatment guidelines, or serve solely as a last resort.[3]The ability to prescribe off-label empowers physicians to innovate within the scope of clinical practice, especially when standard treatments fail.[3] This may offer considerable benefits for patient care. Off-label prescribing avoids the expenses of running clinical trials and obtaining FDA approval for a new indication, which provide pharmaceutical companies with little motivation to seek new approvals for existing medications. In addition, the low incidence and prevalence rates of many dermatologic conditions do not always support extensive research.[1] On the other hand, although off-label prescribing is legal and common, there are concerns regarding safety and efficacy that may need to be addressed, as well as issues of cost to the healthcare system.[3,4]

The field of dermatology is in a unique position to repurpose existing therapies for cutaneous conditions, given the broad variety of pathophysiologic processes affecting the skin. This review covers five medications that have been adapted for novel off-label use within dermatology. We include a brief history of each drug, followed by mechanisms of action, current use in dermatologic practice, and adverse effect profiles.

Dapsone

First synthesized in 1908 during experiments on dye chemistry,[5] dapsone is a sulfone drug that possesses both antimicrobial and anti-inflammatory activities. However, dapsone's medical applications were not discovered for nearly 30 years, when it was shown to possess antistreptococcal activity in mice.[6] About a decade later sulfones were implemented for leprosy[7] and dermatitis herpetiformis,[8] paving the way for further dermatologic applications.

Like sulfonamide antibiotics, dapsone acts bacteriostatically via competitive inhibition of dihydropteroate synthetase (competing with *para*-aminobenzoic acid for the enzyme active site), thereby decreasing downstream production of folic acid.[9] Its anti-inflammatory mechanism is much more complex and enables translation of dapsone to numerous neutrophil-mediated and autoimmune processes.[10]These effects are varied and incompletely characterized, but foremost among them is reversible inhibition of myeloperoxidase, preventing cellular damage by hypochlorous acid produced by both neutrophils and eosinophils.[11]

Dapsone is ideally suited for broad off-label use in dermatology because of its combination antimicrobial-antiprotozoal effects, formidable anti-inflammatory activity, long-term (even lifelong) safety, steroid-sparing properties, and low cost.[12] Currently, dapsone is only approved by the FDA for dermatitis herpetiformis and as a component of leprosy multidrug therapy. Its off-label uses in dermatology stretch much further: dapsone is recommended as first-line therapy for acropustulosis infantilis,[13] cicatricial pemphigoid,[14] erythema elevatum diutinum,[15] IgA pemphigus,[16] linear IgA dermatosis,[17] prurigo pigmentosa,[18] recurrent neutrophilic dermatosis of the dorsal hands,[19] and subcorneal pustulosis.[13] It may be employed as adjunctive therapy in a number of diseases, and reports of use exist for many other conditions, with variable results.[10,20,21] Dosing of dapsone for chronic inflammatory dermatoses is highly individualized, generally beginning at 50-100 mg daily; if treatment goal is not attained after 4-6 weeks, the dose may be titrated up to 150-300 mg daily, according to patient tolerability.[12]

The most common adverse effects associated with dapsone include methemoglobinemia and hemolysis.[10] Severe anemia may occur in persons with glucose-6-phosphate dehydrogenase deficiency. Accordingly, all patients should be screened for this enzyme deficiency prior to initiation of therapy. Cimetidine, by acting as a cytochrome P450 inhibitor, has been shown to reduce methemoglobin formation and may increase adherence among patients receiving more than 200 mg daily.[22]

Doxepin

The first phenothiazine compound was synthesized in 1883 during chemical dye experiments, but no medicinal use was found for this class of drugs until 1952, when exciting results were reported on the use of chlorpromazine for psychosis. This spurred a series of experiments on the emerging class of tricyclic antidepressants, resulting in the creation of doxepin in the early 1960s.[23]

Tricyclic antidepressants such as doxepin act primarily by inhibiting reuptake of serotonin and norepinephrine, increasing the synaptic concentrations of those neurotransmitters. However, there are numerous off-target effects that occur with use of this class of drugs, mediated largely via muscarinic and histamine receptors.[24] Doxepin has 56 times the affinity of hydroxyzine and nearly 800 times that of diphenhydramine for the H1 receptor.[25]

Pruritus is a very common dermatologic complaint. Given doxepin's well known activity at histamine H1 receptors, topical doxepin formulations are FDA-approved for pruritus secondary to eczematous dermatitis. Doxepin has found more extensive use as a systemic agent prescribed to patients suffering from psychodermatoses, especially neurotic excoriations, as

well as generalized pruritus and chronic urticaria.[26] In addition to its antipruritic effects, doxepin possesses sedative activity that proves useful in alleviating these conditions. The overlap between dermatology and psychiatry is not insignificant: the estimated prevalence of psychiatric comorbidity in dermatologic outpatients exceeds 25%.[27] As many patients will balk at a referral to psychiatry,[28] dermatologists should be comfortable using drugs like doxepin to provide relief to patients suffering from psychocutaneous conditions leading to chronic pruritus.

Doxepin therapy starts at 10-25 mg nightly. Antipruritic and sedative effects begin shortly after treatment initiation, even at low doses; depending on patient response, the dose can be increased gradually by 10-25 mg every 2 weeks until a therapeutic maintenance dose providing adequate relief of symptoms is reached (usually 75-300 mg nightly). Complete therapeutic effect, including antidepressant activity, typically takes at least 2 weeks to emerge.[29] Potential adverse events with doxepin use relate to its off-target receptor effects. These include cardiotoxicity, orthostatic hypotension, increased seizure risk, excessive sedation, weight gain, confusion and delirium (especially in the elderly), dry mouth, blurred vision, acute glaucoma crisis, constipation, urinary retention, and sexual dysfunction.[26,29]

Spironolactone

Use of spironolactone began in 1954 as treatment for hyperaldosteronism.[30] Since that time, it has been employed in the settings of hypertension (as a potassium-sparing diuretic), heart failure, ascites secondary to hepatic disease, and hypokalemia. In 1969, investigators discovered anti-androgenic activity of spironolactone in rats, thereby ushering in future dermatologic applications.[31]

As an anti-androgenic agent, spironolactone acts both centrally and peripherally, decreasing production of androgens as well as blocking their effects on target tissues. Specifically, it inhibits steroidogenesis via selective destruction of microsomal cytochrome P450 in the testes and adrenal glands, and acts competitively to block cytosolic receptors on target organs.[32]

Today spironolactone is used off-label in dermatology to manage several androgen-dependent conditions. It is beneficial for acne because both increased androgen levels and heightened sensitivity of sebaceous glands to androgens contribute to disease through increased sebum production. Spironolactone has proven successful as monotherapy in women with cyclic or late-onset acne, and also serves as an adjunct to antibiotics when oral retinoids cannot be used. The dose range for acne is 50-200 mg daily.[33] In the setting of hirsutism, both central overproduction and peripheral sensitization to androgens leads to a shift from fine, non-pigmented vellus hair to thicker, pigmented, coarse terminal hair. In addition to seeking the underlying cause of the hirsutism (polycystic ovarian syndrome, idiopathic, neoplasm, etc.), daily administration of 50-200 mg of spironolactone has demonstrated efficacy.[32,33] Oral contraceptives may act synergistically to decrease unwanted hair.[34] Lastly, although scalp hair growth is not greatly androgen sensitive, spironolactone (50-200 mg daily) improves female pattern hair loss.[32,33] Patients may benefit from addition of 5% minoxidil to their treatment regimen.[35]

Spironolactone's anti-androgenic activity limits use in male patients due to the potential for development of gynecomastia and sexual side effects. In females it may cause breast enlargement and/or tenderness and menstrual changes, including postmenopausal bleeding. Orthostatic hypotension is a concern, especially in patients taking additional blood pressure medications. Severe hyperkalemia is rare in patients with normal renal function and those who are not simultaneously taking other potassium-elevating drugs (e.g., angiotensin-converting enzyme inhibitors). Mild gastrointestinal and neurologic side effects are common. Spironolactone is contraindicated in pregnancy owing to potential teratogenicity.[32,33]

Tetracyclines

Following their discovery as natural fermentation products of *Streptomyces aureofaciens*, the tetracyclines were introduced into clinical medicine in the early 1950s.[36] Tetracyclines exert bacteriostatic activity by binding to the 30S subunit of the bacterial ribosome, thereby inhibiting bacterial protein synthesis. However, over 30 years ago investigators began to recognize that this class of antibiotics could therapeutically modulate other processes, including angiogenesis, cellular proliferation, inflammation, and immunity.[37,38] These numerous desirable properties have since been exploited and the tetracyclines have found widespread use in many dermatologic conditions.[37,39]

Tetracyclines are commonly used in the treatment of acne, and it is now believed that tetracycline, minocycline, and doxycycline display antimicrobial, anti-inflammatory, and fatty acid/lipase-related activities to improve this condition.[40,41] For rosacea and related disorders, both anti-inflammatory and anti-angiogenic effects of tetracyclines may affect disease course.[42] Tetracycline and minocycline, alone or alongside nicotinamide, show efficacy in the setting of bullous dermatoses, specifically those involving the dermoepidermal junction, and may serve as alternatives to systemic corticosteroids.[37,39] For cutaneous sarcoidosis, 8 of 12 patients administered minocycline 200 mg daily for 12 months exhibited complete clearing of lesions, and 2 patients had partial responses.[43] COL-3, a chemically modified tetracycline, was both active and well-tolerated in a clinical trial investigating its use in AIDS-related Kaposi's sarcoma.[44] Tetracyclines are also reported to be helpful in a number of neutrophilic dermatoses, such as Sweet's syndrome and pyoderma gangrenosum; however, the level of evidence is limited and the observed effects need further characterization.[37,39]

Although generally nontoxic and well-tolerated, significant adverse effects may occur with administration of tetracyclines. These include photosensitivity (especially with doxycycline), skin and nail discoloration (minocycline), gastrointestinal upset, vaginal candidiasis, and dizziness (minocycline). Less commonly, minocycline has been associated with more serious complications such as hypersensitivity syndrome reaction, serum sickness-like reaction, and immunologic conditions

TABLE 1.

Drugs Repurposed for Use in Dermatology: Dosing, Uses, and Significant Adverse Events (AEs)

Drug	Dose Range	Dermatologic uses	Significant AEs
Dapsone	50-100 mg daily for 4-6 weeks (can titrate up to 150-300 mg daily)[12]	**FDA approved:** dermatitis herpetiformis, leprosy **Off label:** acropustulosis infantilis,[13] cicatricial pemphigoid,[14] erythema elevatum diutinum,[15] IgA pemphigus,[16] linear IgA dermatosis,[17] prurigo pigmentosa,[18] recurrent neutrophilic dermatosis of the dorsal hands,[19] subcorneal pustulosis[13]	Methemoglobinemia, hemolysis[10] (screen for G6PD deficiency)
Doxepin	10-25 mg nightly; increase by 10-25 mg every 2 weeks to reach therapeutic maintenance dose (usually 75-300 mg nightly)[29]	**FDA approved:** pruritus secondary to eczematous dermatitis (topical formulation) **Off label:** psychodermatoses (neurotic excoriations), generalized pruritus, chronic urticaria[26]	Cardiotoxicity, orthostatic hypotension, increased seizure risk, excessive sedation, weight gain, confusion/delirium (elderly), dry mouth, blurred vision, glaucoma crisis, constipation, urinary retention, sexual dysfunction[26,29]
Spironolactone	50-200 mg daily[33]	**Off label:** acne, hirsutism, female pattern hair loss[32,33]	Gynecomastia, sexual side effects (males); breast enlargement/tenderness, menstrual changes (females); orthostatic hypotension; teratogenicity
Tetracyclines	Doxycycline: 50-100 mg once to twice daily; sub-antimicrobial dose (rosacea): 20 mg twice daily Minocycline: 50-100 mg once to twice daily	**FDA approved:** acne (minocycline), rosacea (doxycycline) **Off label:** acne,[40,41] bullous dermatoses,[37,39] cutaneous sarcoidosis,[43] neutrophilic dermatoses (eg, Sweet's syndrome, pyoderma gangrenosum)[37,39]	Photosensitivity (esp. doxycycline); minocycline: skin/nail discoloration, hypersensitivity syndrome reaction, serum sickness-like reaction, drug-induced lupus, autoimmune hepatitis, polyarteritis nodosa, polyarthritis;[45] teratogenicity, contraindicated in children <9 years
Thalidomide	Erythema nodosum leprum: 100-400 mg daily; aphthous stomatitis and neutrophilic dermatoses: 100 mg daily; recalcitrant discoid or subacute cutaneous lupus erythematosus: 50–100 mg/day, tapered to 25–50 mg/day after clinical effect seen[60]	**FDA approved:** erythema nodosum leprum **Off label:** very effective – aphthous stomatitis,[48] Behçet's syndrome,[49] cutaneous lupus erythematosus,[50] prurigo nodularis;[51] moderately effective – actinic prurigo,[52] adult Langerhans cell histiocytosis,[53] cutaneous sarcoidosis,[54] erythema multiforme,[55] graft-versus-host disease,[56] Jessner lymphocytic infiltrate of the skin,[57] uremic pruritus[58]	Teratogenicity, sedation, dizziness, peripheral neuropathy, thromboembolism, constipation, skin reactions[47,59]

G6PD, glucose-6-phosphate dehydrogenase

including drug-induced lupus, autoimmune hepatitis, polyarteritis nodosa, and polyarthritis.[45] Tetracyclines should not be used in pregnant women or children less than 9 years of age because of effects on bone and cartilage.

Thalidomide

In the early 1950s thalidomide was marketed as an antiepileptic agent and sedative prior to being rebranded as an antiemetic for use during pregnancy. By 1962 it became clear that this substance possessed significant teratogenic properties when used during the first trimester, causing severe anomalies such as phocomelia and long bone defects. General use of thalidomide ceased in the early 1960s, by which point it had caused an estimated 12,000 birth defects, mainly in Germany. However, in 1965 thalidomide was found to be effective for erythema nodosum leprum, and was eventually approved by the FDA for that purpose in 1998. In 2006 it was approved for use in multiple myeloma. The orphan drug status of thalidomide has facilitated its innovative application in many dermatologic conditions.[46,47]

Thalidomide's mechanism of action is not yet fully understood, but it acts through diverse sedative, immunomodulatory, anti-inflammatory, and anti-angiogenic effects.[46,47] Following failure of standard therapy, thalidomide has been used experimentally in numerous dermatologic conditions, found to be very effective in aphthous stomatitis,[48] Behçet's syndrome,[49] cutaneous lupus erythematosus,[50] and prurigo nodularis.[51] It is moderately effective for actinic prurigo,[52] adult Langerhans cell histiocytosis,[53] cutaneous sarcoidosis,[54] erythema multiforme,[55] graft-versus-host disease,[56] Jessner lymphocytic infiltrate of the skin,[57] and uremic pruritus.[58] These are the conditions for which evidence advocating use of thalidomide is strongest; the drug has been piloted in many others, with less convincing results.[47]

Obtaining thalidomide in the United States requires participation in the System for Thalidomide Education and Prescribing Safety (S.T.E.P.S.) program in order to prevent fetal drug exposure. Apart from teratogenesis, thalidomide is commonly associated with sedation, dizziness, peripheral neuropathy, thromboembolism, constipation, and skin reactions.[47,59]

Conclusion

As these examples illustrate, by utilizing off-label prescribing dermatology has discovered innovative means of treating the myriad disease entities that fall within its scope of practice. Off-label prescribing simultaneously avoids the time and expense of running clinical trials for oftentimes rare diseases while offering patients expedient, effective therapeutic

options outside limited FDA-approved regimens.[1] It is important that practitioners and investigators continue to compile evidence supporting off-label applications in order to refine current practices and provide patients with the safest, most successful possible treatment choices.

Disclosures

The authors have no relevant disclosures to declare.

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