Unconventional uses of common conventional drugs: A review

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Introduction

The Oxford English dictionary defines conventional as something "based on or in accordance with what is generally done or believed," whereas, unconventional is referred to as "not based on or not conforming to what is generally done or believed." In the field of science and technology what was unconventional yesterday may, through some technological advance or some ingenious new process, become conventional tomorrow. An unconventional line of thought harbors creativity and at times paves the way for innovative discoveries. In this article, we seek to summarize certain traditionally used conventional drugs employed successfully for some unconventional indications in the field of dermatology.

Implication in Dermatology

Dermatology holds a unique position to repurpose existing conventional therapies unconventionally, given the varied spectrum of the pathophysiologic process affecting the skin. It is not an uncommon practice for dermatologists to treat cutaneous conditions with medications that are not indicated for the specific condition being treated. But such unconventionally used drugs must be rigorously tested for effectiveness and safety by well-designed clinical trials. We can label such evidence-based judiciously employed interventions as unconventional uses of conventional drugs.

What Constitutes an Unconventional Drug Use?

The drug is already approved for usage in another disorder. The use of the drug in its unconventional role is supported by logical mechanistic reasoning but is not yet routine enough to feature in standard textbooks. The drug has been found useful for the condition in a few anecdotal reports.

Dapsone

Currently, dapsone is only approved for dermatitis herpetiformis and as a component of leprosy multidrug therapy. Its anti-inflammatory mechanisms are much more complex and probably work through reversible inhibition of myeloperoxidase. This prevents cellular damage by hypochlorous acid that is produced by both neutrophils and eosinophils. Dapsone is ideally suited for broad off-label uses in dermatology because of its combined antimicrobial effects, anti-inflammatory activity, steroid-sparing properties and low cost. One such purely unconventional use is in erythema annulare centrifugum. In certain cases of erythema annulare centrifugum erythromycin, azithromycin, metronidazole and topical steroids fail to provide an adequate response and there are recurrences with oral steroids. Reports are available of successful treatment with dapsone (100mg twice daily for a fortnight and tapered off over the next 2 weeks) in resistant cases. The ability of dapsone to inhibit mitogen-stimulated lymphocyte transformation, its effects on membrane-associated phospholipid metabolism, lysosomal enzymes and tissue proteinases have been suggested as an explanation for the therapeutic response.[1] In recurrent aphthous stomatitis, dapsone (25 mg/day for 3 days, 50 mg/day for 3 days, 75 mg/day for 3 days and a maintenance dose of 100 mg/day) yielded excellent results in preventing recurrences. Of the patients who reported benefits with dapsone, three remained ulcer-free without medication for 9 months.[2]

Losartan

Losartan is an approved drug for the treatment of hypertension but it has also been shown to be beneficial in some rare diseases manifesting with secondary fibrosis. The rationale is that as an angiotension-1 receptor antagonist, losartan counteracts transforming growth factor beta signaling in a context- and

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disease-specific manner.[3] In dystrophic epidermolysis bullosa (DEB), inflammation and transforming growth factor beta signaling are the major drivers of fibrosis and, therefore, losartan seems promising as a symptom-relief therapy.[4]

Colchicine

Colchicine is an ancient medication that has traditionally been used in the treatment of gout. Interestingly, further clinical applications are being recognized due to its potent anti-inflammatory activity.[5] Recently, Kanwar and Parsad have reported the improvement of patients diagnosed clinically as lichen planus pigmentosus treated with colchicine. They noted 30–80% reduction in the intensity of pigmentation in 20 patients, while no improvement was seen in five patients.[6]

Ondansetron

Ondansetron is a serotonin 5-HT3 receptor antagonist that is effective in the management of nausea and vomiting. One of the postulated mechanisms of cholestatic-induced pruritus involves the serotonin system. Several anecdotal reports outline the successful use of ondansetron and related agents in the treatment of pruritus associated with cholestasis.[7,8] As early as 1995, Schwörer*et al*.[9] attempted to demonstrate the effectiveness of ondansetron in treating pruritus associated with cholestasis in a crossover trial involving 10 adults. They studied the acute effects of an intravenous injection of ondansetron (4 mg or 8 mg) versus saline placebo in adults with cholestatic itch. The severity of itch was judged using an analog scale from 0 to 10. Treatment was considered to be successful if an intensity reduction of ≥50% of itch occured within 2 h of injection of the medication. Ondansetron reduced or abolished pruritus within 30 to 60 min after injection and a 50% reduction of the itch intensity was observed for up to 6 h following the injection of 8 mg. However, in another double-blinded controlled trial, 19 patients with resistant pruritus were randomized to receive either ondansetron 8 mg or placebo as a single intravenous bolus, followed by oral ondansetron 8 mg or placebo twice daily for 5 days. Ondansetron was not found to provide any benefit in the group of pruritic patients during this short-term treatment.[10]

Ivermectin

Ivermectin cream 1% has already been approved by the United States Food and Drug Administration for the treatment of inflammatory lesions of rosacea in 2014. Although the role of *Demodex* mites in the pathogenesis of rosacea (and variants of rosacea such as perioral dermatitis) awaits elucidation, techniques such as reflectance confocal microscopy have demonstrated that decomposing *Demodex* mites correlate with improvement following the application of topical ivermectin. Noguera-Morel *et al*.[11] studied the therapeutic value of using either oral or topical ivermectin in 15 children diagnosed with either papulopustular rosacea or perioral dermatitis. A total of eight patients with papulopustular rosacea and seven with perioral dermatitis were treated with either a single dose of 200 to 250 μg/kg of oral ivermectin or 1% ivermectin cream applied once a day for 3 months. Complete or almost complete clearance was achieved in eight patients treated orally and in six children treated with topical ivermectin. The overall response to topical or oral ivermectin was excellent: 14 of 15 patients achieved complete or almost complete clearance of lesions, 3 of 14 patients experienced relapses and 11 of 14 remained disease-free for a prolonged period.

Allopurinol

Various therapies have been suggested for disseminated granuloma annulare but none were demonstrated to be consistently efficacious. The low prevalence of the disease has further hindered the conduct of randomized controlled studies; therefore, no standard therapy has been defined. Allopurinol has been successfully used in granulomatous diseases such as sarcoidosis, leishmaniasis, trypanosomiasis or reactions to polymethylmethacrylate spheres. About 300mg of allopurinol prescribed twice daily for 2–6 months in three patients with long-lasting, therapy-resistant disseminated granuloma annulare showed marked lesional improvement and disease-free state on regular follow-up.[12,13] Mizuno has suggested that this drug may block granuloma formation by down-regulation of intercellular adhesion molecule-1 and the expression of P2X7 receptors on monocytes which are involved in adhesion and fusion and consequently, in giant cell formation.[14] Interpretation of these findings is, however, complicated by case reports of allopurinol-induced disseminated granuloma annulare. Thus, allopurinol may serve as an alternative drug in therapy-resistant patients, after careful assessment of the risk/benefit ratio, given the frequency of side effects associated with allopurinol.

Tetracyclines

Tetracyclines, discovered as natural fermentation products of *Streptomyces aureofaciens*, exert bacteriostatic activity by binding to the 30S subunit of the bacterial ribosome, thereby inhibiting bacterial protein synthesis. However, over the past 3 decades, investigators have begun to recognize that this class of antibiotics could therapeutically modulate other processes, including angiogenesis, cellular proliferation, inflammation and immunity.[15] These numerous desirable properties have since been exploited and the tetracyclines have found widespread utility in many dermatologic conditions.[15,16]

Tetracyclines are commonly used in the treatment of acne and it is now believed that tetracycline, minocycline and doxycycline possess antimicrobial, anti-inflammatory and fatty acid/lipase-related activities which improve this condition.[17] For rosacea and related disorders, both anti-inflammatory and antiangiogenic effects of tetracyclines may affect disease course.[18] Tetracycline and minocycline, alone or alongside nicotinamide, show efficacy in the setting of autoimmune bullous dermatoses and may serve as alternatives to systemic corticosteroids.[16] For cutaneous

sarcoidosis, eight of 12 patients administered minocycline 200 mg daily for 12 months exhibited complete clearing of lesions and two patients had partial responses.[19] COL-3, a chemically modified tetracycline, was both active and well-tolerated in a clinical trial investigating its use in acquired immunodeficiency syndrome-related Kaposi's sarcoma.[20] Tetracyclines are also reported to be helpful in several neutrophilic dermatoses, such as Sweet's syndrome and pyoderma gangrenosum (mechanism of action is through inhibition of IL-8 and neutrophils); however, the level of evidence is limited and the observed effects need further characterization.[21]

Thalidomide

In the early 1950s, thalidomide was marketed as an antiepileptic agent and sedative before 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. However, in 1965 thalidomide was found to be effective for erythema nodosum leprosum and was eventually approved by the Food and Drug Administration for that purpose in 1998. The orphan drug status of thalidomide has facilitated its innovative application in many dermatologic conditions.[22,23]

Thalidomide acts through diverse sedative, immunomodulatory, anti-inflammatory and anti-angiogenic effects.[22,23] Following the failure of standard therapy, thalidomide has been used experimentally in numerous dermatologic conditions and found to be very effective in aphthous stomatitis,[2,24] Behçet's syndrome,[25] cutaneous lupus erythematosus[26] and prurigo nodularis.[27] It is moderately effective for actinic prurigo,[28] adult Langerhans cell histiocytosis,[29] cutaneous sarcoidosis,[30] graft-versus-host disease,[31] Jessner's lymphocytic infiltrate of the skin[32] and uremic pruritus.[33] These are the conditions for which evidence advocating the use of thalidomide is strongest; the drug has been piloted in many other cutaneous diseases with less convincing results.

Aspirin

Aspirin is among the potential exacerbating agents for mast cell degranulation. However, aspirin can also be a useful treatment for patients with systemic (or cutaneous) mastocytosis who experience attacks caused by mediator release, including the release of prostaglandin D2.[34,35] It has generally been advised that, when used, aspirin initially be administered in small doses to patients with systemic mastocytosis who are already receiving H1 and H2 antihistamine prophylaxis.[36,37] Long-term therapy with aspirin has also been recommended to prevent hypotensive attacks in systemic mastocytosis. Doses of aspirin (3.9–5.2 g/d) that are reportedly effective in normalizing elevated levels of prostaglandin D2 have corresponded to serum salicylate levels of 20–30 mg/dL.[38,39] Interestingly, in a retrospective review of 20 patients with systemic mastocytosis, the doses of aspirin (81mg–500mg administered twice daily) necessary for inhibition of prostaglandin D2 production, as assessed by excretion of the prostaglandin D2 metabolite 11-prostaglandin F2, were found to be lower than those previously reported as necessary for the treatment of systemic mastocytosis. Aspirin administration in systemic mastocytosis patients generally is tolerated without systemic adverse effects, particularly if the patient has a history of prior aspirin use before a diagnosis of systemic mastocytosis has been made.[40]

Itraconazole

Itraconazole displays a great diversity of non-antifungal activity and has been used to treat a broad spectrum of diseases. Itraconazole has been used to treat a variety of advanced cancers. Hydroxy-itraconazole, a metabolite of itraconazole, inhibits the Hedgehog pathway, explaining its effectiveness in advanced basal cell carcinoma.[41] In 2009, an interesting case of serendipitously administered itraconazole leading to significant improvement in sarcomatoid squamous cell carcinoma was reported.[42] Later, Lin *et al*. demonstrated that the anticancer effect of itraconazole in head and neck squamous cell carcinoma occurs mainly through C1GALT1 inhibition.[43] Dermatological utilization of the antiangiogenesis activity of itraconazole is demonstrated by a case series of infantile hemangioma[44] and keloids.[45] Its anti-inflammatory and immunomodulatory properties have found application in the treatment of palmoplantar pustulosis,[46] HIV-associated eosinophilic folliculitis,[47] lichen planus,[48,49] sarcoidosis[50] and mycosis fungoides.[51] Besides, systemic itraconazole has also been successfully used in yellow nail syndrome (induction of nail growth),[52] refractory atopic dermatitis, especially the unique subtype of head and neck dermatitis (reduction of hypersensitivity reaction to *Malassezia* species in these sebum-rich areas),[53,54] and in reducing irritation of calcipotriol when used for scalp psoriasis (elimination of *Malassezia*).[55]

Pentoxifylline

Pentoxifylline is effective for many dermatological conditions both as a primary drug as well as an adjuvant. The cellular and molecular actions of pentoxifylline is exerted through immune modulation, antitumor necrosis factor-α effects, antifibrinolytic effects, along with effects on endothelial cells and adhesion molecules.[56] Studies have documented that pentoxifylline rapidly ameliorates the systemic symptoms of type II leprosy reaction, and may prove to be a good option for patients with HIV coinfection, wherein steroids are contraindicated.[57,58] It has been used as an adjuvant in psoriasis to control abnormal triglyceride metabolism and also in combination with ciclosporin to reduce the side effects of the latter.[59,60] The inhibitory effect of pentoxifylline on tumor necrosis factor-α has contributed to its efficacious use in the papular pruritic eruption of HIV,[61] leishmaniasis,[62,63] graft-versus-host disease[64] and sarcoidosis.[65] Other therapeutic applications include keloids, scleroderma, morphea,[66,67] oral submucous fibrosis,[68] recurrent aphthous stomatitis,[2] actinic

Table 1: Drugs and their indications (approved and unconventional)

Drug	Approved indication	Unconventional uses
Dapsone	Dermatitis herpetiformis MDT for leprosy	Resistant cases of erythema annulare centifugum
Losartan	Hypertension	Dystrophic epidermolysis bullosa
Colchicine	Gout	Lichen planus pigmentosus
Rifampicin	Antitubercular therapy MDT for leprosy Atypical mycobacterial infection	Recalcitrant aphthous stomatitis Cholestatic itch
Ondansetron	Prevention of nausea and vomiting (secondary to emetogenic cancer chemotherapy, radiotherapy and postoperative)	Cholestatic itch
Opioid antagonists (Naloxone, Naltrexone)	Opioid overdose Reversal of opioid-induced respiratory depression Maintenance therapy for opioid and alcohol use disorders	Cholestatic itch
Ivermectin	Onchocerciasis Intestinal strongyloidiasis Head lice infestation (topical) Rosacea (topical)	Perioral dermatitis
Allopurinol	Gout Prevention of tumor lysis syndrome, recurrent calcium nephrolithiasis	Disseminated granuloma annulare
Tetracycline	Bacterial infections	Rosacea Autoimmune bullous dermatoses Granulomatous diseases (sarcoidosis, foreign body granulomas, granulomatous cheilitis) Neutophilic dermatoses (Sweet syndrome, pyoderma gangrenosum) acquired immunodeficiency syndrome-related Kaposi sarcoma
Thalidomide	Multiple myeloma Type II lepra reaction	Recalcitrant aphthous stomatitis Behçet's syndrome Prurigo nodularis Cutaneous lupus erythematosus
Aspirin	Coronary heart disease Stroke Kawasaki disease Acute rheumatic fever	Systemic mastocytosis
Itraconazole	Fungal infections	Anticancer agent Infantile hemangioma Yellow nail syndrome Keloid HIV-associated eosinophilic folliculitis Lichen planus Palmoplantar pustulosis Sarcoidosis Mycosis fungoides Refractory atopic dermatitis (head and neck) Reducing calcipotriol irritation in scalp psoriasis
Pentoxifylline	Intermittent claudication	Recalcitrant aphthous stomatitis Type II Lepra reaction with HIV coinfection Psoriasis (amelioration of renal toxicity of cyclosporine and to control abnormal triglyceride metabolism) Papular pruritic eruption of HIV Leishmaniasis Graft versus host disease Sarcoidosis
Naltrexone	Opioid overdose Reversal of opioid-induced respiratory depression Maintenance therapy for opioid and alcohol use disorders	Hailey-Hailey disease
Tranexamic acid	Heavy menstrual bleeding Short-term prevention in patients with hemophilia	Melasma
Clofazimine	MDT for leprosy Type II lepra reaction	Recalcitrant aphthous stomatitis

MDT: Multidrug therapy

prurigo,[69] lipodermatosclerosis[70] and generalized granuloma annulare.[71]

Naltrexone

Improvement of Hailey-Hailey disease with low-dose naltrexone (4.5 mg daily) has been reported, but relapse after cessation of therapy remains a common problem. Cao *et al*.[72] found a variable response even after using higher doses (12.5–50 mg daily). The proposed mechanism of action is the inhibition of the μ-opioid receptor in the skin and toll-like receptor 4 antagonism.

Tranexamic Acid

The skin-whitening effects of tranexamic acid (TXA) were incidentally found when it was used in the treatment of aneurysmal subarachnoid hemorrhage. For treating hyperpigmentation, the drug may be administered orally, topically, intradermally or intravenously. In the prospective, randomized controlled trial conducted by Karn *et al*.,[73] oral tranexamic acid was administered to patients of melasma, at a dose of 250 mg twice daily for 3 months. A statistically significant decrease in the mean melasma area and severity index from the baseline was observed. The authors concluded that it provides rapid and sustained improvement in the treatment of melasma. The dose of oral tranexamic acid used in melasma is far less than that prescribed for its hemostatic action. Kanechorn Na Ayuthaya *et al*.[74] conducted a double-blind randomized controlled trial among Asians and used 5% tranexamic acid in a liposome gel formulation for epidermal melasma for 12 weeks. This was compared with the vehicle in a split-face trial. Even though 78.2% of patients showed a decrease in the melanin index, the results were not significant as compared with the vehicle. The dermal and mixed variants of melasma are highly treatment-resistant. In this case, tranexamic acid may be administered intradermally. The microneedling method proves to be efficacious in the intradermal delivery of the drug. Another notable application is the intravenous administration of tranexamic acid[75] for skin lightening where a dose of 500 mg/week is administered for a period of 1–2 months and 500 mg every month for maintenance. The proposed mechanism of action is the downregulation of the vascular component of melasma. Tranexamic acid prevents ultraviolet-induced pigmentation by interfering with the binding of plasminogen to the keratinocyte. This reduces the levels of free arachidonic acid, thereby leading to a reduction of prostaglandins in the melanocytes. Tranexamic acid also prevents angiogenesis by blocking the action of plasmin.

Clofazimine

Clofazimine is an antimicrobial drug, used for the treatment of leprosy in combination with other drugs such as rifampicin and dapsone. In severe recurrent aphthous stomatitis, clofazimine at a dose of 100 mg/day for 6 months was found to prevent the appearance of new lesions.[76]

The drugs and their indications (both approved and unconventional) have been summarized in Table 1.

Conclusion

As these examples illustrate, by utilizing off-label prescribing of various drugs, dermatologists have discovered innovative means of treating the myriad disease entities that fall within the scope of their practice. Off-label prescription simultaneously avoids the time and expense of running clinical trials for rare diseases while offering patients expedient, effective therapeutic options outside limited drug authority-approved regimens. Practitioners and investigators must continue to compile evidence supporting off-label applications to refine current practices and provide patients with the safest, most successful possible treatment choices. We would also like to mention that any innovation must be supported by good quality evidence generation, to avoid any serious adverse reactions in the future, one of the examples being the questionable role of thalidomide in the treatment of toxic epidermal necrolysis. Moreover, in the current COVID-19 pandemic a lot of molecules like hydroxychloroquine, azithromycin, ivermectin etc., have been tried with a hope to get satisfactory results. They have all flattered to deceive, after being subjected to the rigours of randomized controlled trials. We should always remember that in the quest for finding out an "effective drug," "safety" and "tolerability" should not be shown the back door, and that the randomized controlled trial remains the gold standard to determine effectiveness.

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Conflicts of interest

There are no conflicts of interest.

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