# Therapeutic Update on Topical Steroid Withdrawal

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***Abstract:*** **Topical steroid withdrawal syndrome (TSW) is an emerging iatrogenic condition increasingly reported in patients following prolonged topical corticosteroid use, particularly among those with atopic dermatitis (AD). Despite rising awareness, TSW remains controversial and under-recognized due to its lack of formal diagnostic criteria and overlap with poorly controlled AD. In response to the growing demand for guidance, we review a wide range of treatments currently being used or studied for TSW, including pharmacologic therapies, natural products, lifestyle interventions, and alternative approaches such as acupuncture and dietary modifications. While many strategies show benefits, few are supported by rigorous clinical evidence. This article aims to provide clinicians and patients with a reference of existing treatment options, highlight areas of uncertainty, and call for further research into validated, evidence-based therapies for this condition.**

## Capsule Summary

- Topical steroid withdrawal syndrome (TSW) is an under-recognized condition affecting a portion of patients using topical corticosteroids.
- TSW carries a high psychosocial burden and often leads to patient frustration due to lack of formal recognition.
- This article provides an overview of available treatments and emphasizes the need for more clinical research to guide evidence-based care.

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## INTRODUCTION

Topical steroid withdrawal syndrome (TSW) is a poorly understood condition that is characterized as arising after discontinuation of topical corticosteroids (TCS), typically after prolonged use. TCS are routinely used to manage chronic inflammatory skin diseases such as atopic dermatitis (AD), psoriasis, and contact dermatitis due to their anti-inflammatory and anti-pruritic properties. However, inappropriate or extended use can lead to what may constitute a form of physical dependence and, upon withdrawal, trigger a reaction known as TSW or, historically, "Red Skin syndrome".[1] This condition is gaining increased attention as awareness grows around the concept of topical steroid addiction and withdrawal reactions, a trend amplified by discussions on social media platforms and patient advocacy forums.[2]

TSW manifests in two major clinical variants: erythematoedematous and papulopustular.[3] The erythematoedematous type tends to arise in individuals with chronic eczema and is marked by pronounced erythema, increased cutaneous temperature, and dermal edema.[3] The papulopustular type more closely resembles rosacea, presenting with papules, pustules, and deep dermal nodules, while findings such as edema or dysesthesia are less prominent.[3,4] While predominantly associated with more potent steroids applied to delicate areas such as the face and genitals, multiple reports demonstrate that symptoms can affect the entire body, even including areas never directly treated.[3,5–7]

Clinically, patients who may be experiencing TSW present with features such as widespread erythema, sharply demarcated "red sleeves," anhidrosis, and other features, though formal diagnostic criteria have not yet been agreed upon.[5] Additional symptoms may include paresthesia-like pain sensations dubbed "zingers" by patients, fluctuations in body temperature, and visible changes such as sagging skin in body

folds or "elephant wrinkles," hair thinning, and pronounced skin shedding.[5,8] Symptoms often continue long after discontinuation of steroids, with an average reported duration of over 47 months.[5]

The pathogenesis of TSW remains unknown, but may be multifactorial, involving metabolic, immunological, and vascular components. A recent study suggests that mitochondrial dysfunction, especially increased activity of complex I, leads to excessive nicotinamide adenine dinucleotide ($NAD^+$) oxidation and disrupts energy production and immune signaling.[5] This dysregulation promotes a proinflammatory state and has been observed in both skin tissue and serum of TSW patients through metabolomic and transcriptomic analyses.[5]

Beyond mitochondrial dysfunction, chronic use of topical steroids can cause epidermal thinning and upregulation of skin enzymes and keratinocyte-derived proteins, such as thymic stromal lymphopoietin (TSLP).[9,10] TSLP plays a role in shifting the immune system toward a Th2-dominant response, mirroring immune imbalances seen in AD.[10] Long term steroid exposure also alters the expression of glucocorticoid receptors (GRs) on immune cells, particularly reducing the GR-α to GR-β ratio, which may contribute to steroid resistance.[11] Beyond good stewardship of TCS with an eye towards prevention of TSW, it is critical to revisit potential therapeutic strategies for those with the presumptive diagnosis of TSW. Although the cornerstone of TSW management is the complete avoidance of steroids in all forms, a variety of non-steroidal therapeutic approaches have been explored to help provide relief. These include systemic agents, topical treatments, natural products, and integrative therapies. While these therapies vary widely in clinical rigor and mechanistic plausibility, many are actively used by patients despite limited clinical guidance.

To reflect this spectrum, therapies with direct clinical evidence in TSW, such as case reports, case series, or open-label trials, are listed in Table 1. In addition to evidence-based interventions, there are numerous supportive therapies frequently utilized that lack TSW-specific evidence. These are summarized in Table 2 to illustrate the breadth of approaches circulating among patients and providers. Table 2 is not intended as a recommendation but rather as a demonstration of the current gap between commonly used supportive measures and the paucity of research on their efficacy. We focused on therapies that have been used specifically in the context of TSW, especially those with published case reports, case series, or mechanistic rationale.

A comprehensive literature review was conducted using PubMed, Embase, and the Cochrane Library to evaluate emerging therapies for TSW. Search terms included "Topical Steroid Withdrawal," "Red Skin Syndrome," "TSW treatment," along with specific interventions such as "black tea compress," "cryotherapy," "dupilumab," "metformin," "berberine," "balneotherapy," and "phototherapy." Eligible studies included randomized controlled trials, observational studies, case series, and mechanistic reports addressing the safety, efficacy, or biological rationale for each therapy. Data extraction focused on clinical outcomes, symptom relief, safety profiles, and mechanistic insights relevant to TSW pathophysiology.

## TSW THERAPIES

### TCS Discontinuation

TCS discontinuation is the cornerstone of treatment for patients experiencing TSW. However, the process is often marked by a rebound reaction characterized by worsening erythema, burning, and discomfort shortly after cessation. This rebound is thought to result from the sudden loss of corticosteroid-induced vasoconstriction, leading to reactive vasodilation.[12] Due to the intensity of this rebound, some clinicians recommend oral steroid use with or without a TCS that has tested negative on patch testing.[13] Nevertheless, current literature remains inconclusive on whether tapering off TCS or abrupt discontinuation yields better outcomes in TSW management.

Historically, TCS removal has been a first-line approach in managing patients suspected of experiencing TSW. Early reports, such as Rapaport's 1999 series of 100 cases, documented that most patients achieved clearance within a few months to two years after discontinuing long-term TCS, with the majority remaining free of recurrent rash during extended follow-up.[80] More recently, a large prospective study by Fukaya et al. involving over 300 patients found substantial improvement after TCS cessation, 75% of infants, 52% of children, and 80% of adolescents and adults improved, with nearly 25% of infants achieving complete remission by study end.[81] Beyond these studies, a substantial body of literature has documented the clinical course of TCS discontinuation across diverse populations.[14,82,83] Collectively, these reports demonstrate that TCS discontinuation has been practiced for decades but continues to exhibit considerable variability in presentation and outcomes.

### Berberine

Berberine (BBR), a plant-derived isoquinoline alkaloid, demonstrates broad therapeutic potential due to its multifaceted antioxidant, anti-inflammatory, and antimicrobial effects, making it a promising agent in dermatologic and systemic inflammatory conditions. Mechanistically, BBR acts primarily by inhibiting mitochondrial complex I, which activates adenosine monophosphate–activated protein kinase (AMPK) and inhibits nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), two pathways that regulate proinflammatory responses.[15,16] Through these mechanisms, BBR downregulates key inflammatory mediators including interleukin-1 beta (IL-1β), interleukin-6 (IL-6), monocyte chemoattractant protein-1 (MCP-1), tumor necrosis factor alpha

**TABLE 1. Topical Steroid Withdrawal Syndrome Therapies with Direct Clinical Evidence**

| Intervention | Study Type | Dose | Outcome Measure (s) | Efficacy | Adverse Effects |
|---|---|---|---|---|---|
| TCS discontinuation[12–14] | Case Series; cohort studies (n = 100–300) | N/A | Time to resolution, symptom course, photographic documentation, symptom-specific recovery (eg, pruritus, anhidrosis) | Most patients achieved partial or complete remission over months to 2 years; 75% infants, 52% children, 80% adolescents/adults improved | Withdrawal-associated flare: severe burning, erythema, edema, inability to tolerate emollients, fatigue, and emotional distress |
| Berberine[5,15–19] | Open-label pilot study (n = 9) | Oral berberine, dose not standardized, purchased online | Patient-reported global improvement; standardized clinical photographs; skin transcriptomics | Did not reduce basal proliferation or ECAR but was a more potent inhibitor of OCR | None reported |
| Topical ruxolitinib[20,21] | Case Report | 1.5% cream once daily | Symptom resolution (erythema, burning, itching, plaques) | Complete clearance within 3 months; flare free ≥5 months | None reported |
| Dupilumab[22–24] | Case series (n = 5) | 600 mg loading dose followed by 300 mg every 2 weeks | BSA, IGA | All patients improved: mean BSA reduced from 61% to 16%; IGA from 3.6 to 1.8 | None reported |
| Traditional Chinese medicine[25–28] | Case series (n = 5) | Personalized herbal regimens, 3–13 months | Resolution of 5 acute symptoms: erythroderma, thermodysregulation, oozing, itch/pain, sleep disturbance | 2/5 near-complete resolution; 3/5 improved thermodysreg-ulation and sleep | None reported |
| Metformin[5,29] | Open-label pilot study (n = 3) | 500-1000mg/day | Patient-reported improvement; standardized clinical photographs | Prevented basal cell hyperproliferation and normalized both OCR and ECAR in HFSCs | None reported |
| Cyclosporine[7,30,31] | Case report (n = 1); Case series (n = 1500) | 4mg/kg/day; 200–500 mg/day | Clinical resolution of erythroderma, normalization of inflammatory markers, symptom relief | Gradual remission in severe erythroderma; moderate symptomatic relief of inflammation in severe withdrawal | Nephrotoxicity, hypertension, neurotoxicity, hypertrichosis |

*BSA, body surface area; ECAR, extracellular acidification rate; HFSCs, human follicular stem cells; IGA, Investigator's Global Assessment; N/A, not applicable; OCR, oxygen consumption rate.*

**TABLE 2. Topical Steroid Withdrawal Syndrome Therapies Without Direct Clinical Evidence**

| Intervention | Dose | Mechanism of Action | Adverse Effects |
|---|---|---|---|
| Doxycycline[32] | 40–200 mg | Bacteriostatic; reversibly inhibits protein synthesis by binding the 30S ribosomal subunit | Nausea, vomiting, abdominal pain, diarrhea; contraindicated in pregnancy due to potential harm to fetal development |
| Erythromycin[33] | Adults: 250–500 mg tablets<br>Kids: 30–50 mg/kg/day | Bacteriostatic; inhibits bacterial protein synthesis by binding to the 50S ribosomal subunit | Nausea, vomiting, abdominal pain, and diarrhea, particularly at higher doses |
| Calcineurin inhibitors[34,35] | 0.03% or 0.1% | Inhibits calcineurin to block NFAT activation, reducing IL-2 transcription and suppressing T-cell-mediated inflammation | Skin burning and pruritus, especially early in treatment; typically transient |
| Antihistamines[36,37] | 12.5–25 mg | Blocks H1 histamine receptors to reduce inflammation, pruritus, and allergic symptoms | Drowsiness (especially with first-generation agents), dry mouth, dizziness, and GI upset |
| Phototherapy[38,39] | Ultraviolet A1 (UVA1) (340–400 nm)<br>Narrowband ultraviolet B (NB-UVB) (311–313 nm) | UVA1 induces T-cell apoptosis and suppresses cytokines; NB-UVB reduces inflammation, enhances skin barrier, and limits *S. aureus* colonization | UVA1: carcinogenic and photoaging; NB-UVB: erythema, sunburn, and xerosis |
| Thermal water[40–42] | Water mineral content of at least 1 g/L | Anti-inflammatory, immunomodulatory, and antioxidant effects; enhances skin barrier and reduces cytokines | None reported |
| Cryotherapy[43–45] | N/A[a] | Enhances antioxidant capacity and reduces inflammation and pruritus via cold-induced upregulation of antioxidant enzymes | Frostbite, skin necrosis, and neuropathy |
| Bland emolient[46–48] | 250–500g weekly | Restores skin hydration and barrier function by forming an occlusive layer that reduces transepidermal water loss and enhances corneocyte water retention | None reported; well tolerated even in sensitive populations |
| Aluminum acetate wet dressings[49] | 3–5% | Topical astringent that reduces inflammation, dries weeping lesions, and provides antimicrobial and antipruritic effects | None reported |
| Apple cider vinegar[50–52] | Typically diluted to 1%–10% for topical use | Acidifies the skin to restore pH and exhibits antimicrobial activity against bacteria and fungi | Skin irritation in sensitive or eczematous skin; may trigger contact dermatitis due to increased nickel ion release |
| Colloidal oatmeal (*Avena sativa*)[48,53] | 1% | Anti-inflammatory and antioxidant effects via avenanthramides; restores moisture, reinforces the skin barrier, and buffers skin surface pH | No serious adverse events reported; generally well tolerated, including in sensitive and pediatric populations |
| Sulfur[54,55] | 1%–10% | Keratolytic and antimicrobial; converted to hydrogen sulfide in the skin, promoting exfoliation and reducing microbial colonization | Malodor, dryness, and potential irritation |
| Sodium sulfacetamide[54,56] | 10% with 5% sulfur | Bacteriostatic inhibition of folic acid synthesis via para-aminobenzoic acid (PABA) antagonism; combined with sulfur for keratolytic and antimicrobial effects | Mild, transient dryness, itching, or irritation |
| Topical metronidazole[57,58] | 0.25%, 0.75%, 1% cream, gel, lotion | Anti-inflammatory and antioxidant; reduces reactive oxygen species and immune-mediated inflammation, leading to decreased erythema and flare severity | Mild skin irritation, dryness, and potential for allergic contact dermatitis |
| Topical clindamycin[59,60] | 1%–2% | Inhibits bacterial protein synthesis by binding to 23S rRNA of the 50S ribosomal subunit, thereby halting translation and exerting bacteriostatic effects | Increased antibiotic resistance, particularly *Staphylococcus aureus* resistance with prolonged or widespread use |
| Topical minocycline[59,60] | 1.5% or 4% | Inhibits bacterial protein synthesis by binding to the 30S ribosomal subunit, offering broad-spectrum antibacterial effects against Gram-positive and Gram-negative bacteria | Headache, diarrhea, initial vertigo, drug-induced lupus |
| Hydrocolloid patches[61,62] | N/A[a] | Creates a moist, occlusive environment by absorbing exudate and forming a gel, while protecting lesions from external irritants and pathogens | Minimal; may cause mild skin irritation or redness, especially with strong adhesives or improper removal |
| Topical cannabidiol (CBD)/ cannabinoids[63,64] | Varies; 1–5% in topical formulation | Inhibits adenosine uptake, enhancing A2A receptor signaling to reduce inflammation, oxidative stress, and mast cell activation | Skin irritation or allergic contact dermatitis, especially with prolonged or high-concentration use |

(*continued*)

**TABLE 2.** (*Continued*)

| Intervention | Dose | Mechanism of Action | Adverse Effects |
|---|---|---|---|
| Personalized probiotic supplements[65] | N/A[a] | Restore microbiome balance and diversity by targeting individual dysbiosis patterns; enhance skin barrier function and modulate immune responses | Not well-established; long-term safety unknown, with variability in response based on individual microbiota and formulation |
| Dietary changes[65] | N/A[a] | Modulates systemic inflammation and supports gut-skin axis by eliminating pro-inflammatory foods and increasing intake of nutrient-dense, microbiome-supportive whole foods | None established |
| Lifestyle Changes[65,66] | N/A[a] | Reduces stress and modulates immune and neuroendocrine responses through habits like exercise, sunlight exposure, mindfulness, and time in nature | None established; considered safe and beneficial when tailored to individual capacity |
| Acupuncture Therapy[67–70] | N/A[a] | Modulates central and peripheral itch signaling by reducing activity in brain regions linked to pruritus and regulating inflammatory cytokines | Localized pain, bruising, infection, or rare serious complications (eg, pneumothorax, cardiovascular injury) typically due to improper technique or non-sterile equipment |
| Black tea[71,72] | N/A[a] | Antioxidant and antibacterial effects via polyphenols like theaflavins, catechins, and hydroxybenzoic acid; these compounds scavenge reactive oxygen species and disrupt bacterial membranes, potentially benefiting inflammatory and aging-related skin conditions | None established for dermatologic use |
| Coal Tar[73,74] | 0.02–2% | Activates the aryl hydrocarbon receptor, promoting epidermal differentiation and filaggrin expression, while suppressing IL-4/STAT6 signaling to reduce Th2-mediated inflammation | Folliculitis, irritation, or photosensitivity |
| Methylene Blue[75] | 1–2 mg/kg (IV), unclear dosing orally | Inhibits nitric oxide synthase and soluble guanylate cyclase, reducing cyclic guanosine monophosphate (cGMP)-mediated vasodilation | Blue discoloration of skin and urine, nausea, dizziness, headache, serotonin syndrome, hemolytic anemia in glucose-6-phosphate dehydrogenase (G6PD) deficiency |
| Cold atmospheric plasma Therapy[76–79a] | Device-dependent; typically administered via direct irradiation or contact treatment | Generates reactive oxygen and nitrogen species that promote cellular regeneration, enhance wound healing, eradicate bacteria and fungi, and reduce inflammation | Transient erythema, mild stinging, dryness, or irritation; long-term safety in TSW unestablished |

[a]N/A indicates that dosing is not applicable or not standardized for non-pharmacologic interventions.
"a" and applied consistently to all non-pharmacologic interventions.

(TNF-α), prostaglandin-endoperoxide synthase 2 (cyclooxygenase-2) (PTGS2), caspase-3 (CASP3), and mitogen-activated protein kinase 1 (MAPK1), particularly in macrophages and monocytes exposed to *Staphylococcus aureus*, helping to reduce bacterial overgrowth.[15–17]

A recent multi-omics analysis of skin and serum from patients with TSW identified several characteristic metabolic and inflammatory abnormalities, including upregulation of mitochondrial complex I activity, increased $NAD^+$ oxidation, and enhanced tryptophan catabolism to kynurenine, alterations previously linked to corticosteroid exposure in both human and in vitro models.[5] These molecular changes were correlated with hallmark TSW symptoms such as flushing, burning, and temperature dysregulation. To explore a targeted therapeutic approach, an open-label pilot study investigated the efficacy of mitochondrial complex I inhibitors in treating TSW.[5] In this study, nine patients elected to use BBR purchased online, and it was associated with measurable clinical improvements. Clinical improvement was evaluated using patient-reported outcome measures and standardized clinical photography. Across both treatment groups, participants reported global symptom improvement, and the overall change was statistically significant per the authors, though they present this data in a pooled fashion with metformin (see below).[5] In addition to reductions in rash severity, patients frequently described their skin as becoming "softer" and "smoother," along with an "inside-out" resolution of pruritus, where deeper, more intense itching subsided before superficial itch. Although flares triggered by infection, stress, or temperature persisted, they were generally milder and shorter in duration than before treatment. In comparison to metformin, in vitro work suggests that BBR is a more potent inhibitor of oxygen consumption rate (OCR) but does not reduce human follicular stem cell (HFSC) hyperproliferation or basal extracellular acidification rate (ECAR), indicating a narrower metabolic effect profile. These findings suggest that BBR may offer therapeutic benefit in TSW by reversing corticosteroid-induced mitochondrial and immune dysregulation.

Despite these potential benefits, BBR is associated with adverse effects including gastrointestinal upset and transient increases in plasma bilirubin levels.[18] Additionally, BBR should

be avoided during pregnancy and in neonates, as it may displace bilirubin from albumin-binding sites, potentially increasing the risk of bilirubin toxicity.[19]

## Topical Ruxolitinib

Topical ruxolitinib 1.5% cream, a selective JAK1/JAK2 inhibitor, has emerged as a potential adjunct therapy for managing TSW. Its mechanism involves interrupting proinflammatory cytokine signaling, particularly within the JAK-STAT pathway, which may help dampen the rebound cytokine cascade believed to contribute to TSW pathogenesis.

Clinical support for ruxolitinib use in TSW is highlighted in a recent case report of a 69-year-old woman with a 5-year history of chronic facial dermatitis and prolonged TCS use.[20] After unsuccessful trials of other non-steroidal topicals including tacrolimus 0.1% ointment and pimecrolimus 1% cream, both of which exacerbated symptoms, she began once-daily treatment with ruxolitinib 1.5% cream. Within three months, she achieved complete clearance of erythema, plaques, burning, and itching, and was able to discontinue corticosteroids entirely. Importantly, she remained flare-free on daily ruxolitinib monotherapy for at least five months, with plans to taper slowly thereafter. This case not only underscores the potential role of topical JAK inhibition as an effective steroid-sparing therapy in TSW but also illustrates its tolerability and sustained benefit in a chronic, refractory case. While some individuals may experience paradoxical eczematous reactions to JAK inhibitors, this patient tolerated the treatment well with no recurrence of symptoms after steroid cessation.[21] However, ruxolitinib cream is costly and may not be readily accessible to all patients due to limited insurance coverage, which should be considered when evaluating its role in TSW management.

## Dupilumab

Dupilumab is a monoclonal antibody that works by blocking the interleukin-4 (IL-4) receptor alpha subunit, thereby inhibiting both IL-4 and IL-13 signaling, which are central to type 2 inflammatory pathways.[22] In the setting of TSW, dupilumab may be considered in patients with concurrent or underlying AD, especially when conventional therapies are poorly tolerated or ineffective. However, like topical ruxolitinib, its high cost and limited insurance coverage may restrict accessibility for many patients, which should be considered when discussing treatment options.

A retrospective case series of five adults with clinically suspected TSW demonstrated consistent clinical benefit from dupilumab, administered as a 600 mg loading dose followed by 300 mg every two weeks.[23] All patients experienced marked reductions in both body surface area (BSA) involvement and Investigator's Global Assessment (IGA) scores, with treatment durations ranging from approximately 9–31 weeks. Notably, mean BSA improved from 61% at baseline to 16%, and mean IGA scores decreased from 3.6 to 1.8, underscoring the potential of dupilumab to effectively reduce disease severity in this population. These findings support further investigation of dupilumab as a therapy for TSW, especially in the context of moderate to severe AD. While generally well tolerated, common side effects include injection site reaction and conjunctivitis.[2]

## Traditional Chinese Medicine (TCM)

Traditional Chinese Medicine (TCM) utilizes mixtures of various herbal compounds, often administered both orally and topically, to modulate inflammation and restore physiological balance. In the context of inflammatory skin conditions such as TSW, TCM formulations commonly incorporate herbs with anti-inflammatory, antimicrobial, and immunomodulatory effects.[25] Studies have identified active ingredients such as *Radix Lithosperm* and *Sophorae Flavescentis*, which downregulate inflammatory cytokines like IL-4, IL-6, and TNF-α, targeting pathways implicated in eczema and steroid withdrawal flares.[26,27]

A recent case series of five adult women with clinically diagnosed TSW explored the effects of individualized TCM regimens administered over 3 to 13 months.[28] All patients had a history of prolonged TCS use and presented with hallmark features of TSW. TCM therapy was tailored to each patient's evolving symptom profile, and effectiveness was assessed based on resolution of five acute symptoms: erythroderma, thermodysregulation, oozing, itch/pain, and sleep disturbances. Two of five patients achieved complete or near-complete resolution of acute symptoms, while the remaining three experienced improvements in thermodysregulation and sleep quality but had continued itch, pain, and erythema. Notably, these benefits were observed despite prior failure of conventional therapies, including calcineurin inhibitors, systemic steroids, and phototherapy. However, the case series lacked standardized dermatologic outcome measures such as the IGA and lacked standardized treatment across patients. Broader integration of TCM into dermatologic care remains limited by the absence of large-scale randomized trials, safety and standardization of herbal compounds, and variability in prescribing practices. Nevertheless, this series suggests that individualized herbal medicine may offer relief in TSW, even for patients who have not responded to conventional approaches.

## Metformin

Metformin has been investigated as a potential therapeutic agent for TSW due to its inhibition of mitochondrial complex I, similar to BBR.[29] In the multi-omics analysis by Shobnam mentioned above for the use of BBR in TSW, metformin treatment of hair follicle stem cells was found to prevent excessive cell proliferation and restore normal mitochondrial function, including both oxygen consumption and extracellular acidification rates.[5] In contrast, BBR did not affect cell proliferation or acidification but more strongly suppressed oxygen consumption, even at lower concentrations.[5] This highlights that while both compounds

inhibit mitochondrial complex I, metformin has broader effects on cellular metabolism and proliferative regulation compared with BBR in vitro.

As noted above from the same open-label pilot study, three patients elected to take metformin prescribed by their primary care providers.[5] Like BBR, metformin also showed clinical benefit in TSW, though the mechanistic profiles differed. In vitro, metformin prevented HFSC hyperproliferation and normalized basal OCR and ECAR, effects not seen with BBR. Clinically, patients on metformin reported improvements in rash severity and reductions in flare intensity and duration, though responses were somewhat less pronounced overall compared to those taking BBR. Importantly, the small numbers preclude deeper analysis.

### Cyclosporine

Cyclosporine, a systemic calcineurin inhibitor, has been among the earliest systemic therapies applied to severe TSW cases. Mechanistically, cyclosporine suppresses T-cell activation by inhibiting IL-2 transcription (via calcineurin blockade), which in turn reduces downstream cytokine-mediated skin inflammation.[30] This immunomodulation may help restrain the exaggerated inflammatory response that occurs during withdrawal, especially when traditional topical agents are insufficient.

The efficacy of cyclosporine was noted by Horiuchi in 2000, who described a 68-year-old patient with erythroderma secondary to steroid withdrawal who achieved gradual remission over ten months with low-dose cyclosporine (4 mg/kg/day) in combination with intermittent ACTH therapy.[31] Clinical improvement correlated with normalization of inflammatory markers and reduction of eosinophilia, suggesting that cyclosporine's immunosuppressive effect stabilized immune overactivation during steroid withdrawal.

Rapaport reviewed over 1500 patients with corticosteroid addiction and withdrawal and noted cyclosporine's selective use in those with severe erythema and inflammation.[7] Administered at doses of 200–500 mg/day for 2–3 months, cyclosporine offered moderate symptomatic relief but did not address the persistent erythema. The authors emphasized that long-term recovery depended on complete steroid cessation and physiologic vascular normalization, rather than continued immunosuppression.

In modern practice, cyclosporine is typically considered a bridging, supportive therapy rather than a curative intervention in TSW. Its benefits are limited to symptom suppression; it does not directly reverse the vascular dysregulation (eg, NO-mediated vasodilation) underlying the "red skin" rebound seen after steroid withdrawal. Because of its risks (nephrotoxicity, hypertension, immunosuppression), its use must be closely monitored.

## DISCUSSION AND CONCLUSION

TSW is an increasingly recognized iatrogenic condition that poses a serious quality-of-life burden for patients previously treated with prolonged or high-potency topical corticosteroids. While seemingly rare, some estimates suggest that 12% to as high as 79% of AD patients may develop TSW, indicating many unknowns that warrant further investigation and awareness among providers.[6,84] Beyond physical symptoms, the psychosocial impact of TSW is substantial. It has been reported that up to 47% of individuals with TSW experience suicidal ideation, underscoring the importance for supportive mental health interventions alongside dermatologic care as well as the importance of recognizing TSW as a serious and distinct clinical entity.[84]

This review highlights a wide array of therapeutic strategies, ranging from repurposed prescription agents to natural remedies and lifestyle interventions, currently being explored by patients and healthcare practitioners. While many of these approaches show promise, few are supported by robust clinical evidence. In addition, newer agents such as dupilumab and topical ruxolitinib, although promising, are associated with high cost and limited insurance coverage, which restricts access for many patients and must be considered when evaluating treatment options. Despite these challenges, the diversity of options reflects a strong patient demand for alternatives amid limited guidance. This article aims to serve as a reference for currently available therapies, identify gaps in the literature, and encourage future controlled studies to validate effective interventions and improve care for this underserved population.

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