



Steroid Phobia: Is There a Basis? A Review of Topical Steroid Safety, Addiction and Withdrawal

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Abstract

There is a growing concern amongst patients about topical corticosteroid (TCS) side effects, with increasing discussion of topical steroid addiction (TSA) and topical steroid withdrawal (TSW) particularly on social media platforms. However, the acceptance of TSA/TSW as a distinct condition remains controversial within the dermatological community. We conducted a literature search using PubMed, MEDLINE, Cochrane Library, Google Scholar, Embase and Web of Science to identify original articles addressing TSA/TSW. We described the definition and reported clinical features of TSA/TSW including its classification into erythematous-edematous and papulopustular subtype. To assess the validity of TSA/TSW, we summarised and objectively appraised the postulated mechanisms for this condition, including tachyphylaxis, dysregulation of glucocorticoid receptors, rebound vasodilation and impaired skin barrier leading to a cytokine cascade. Understanding the evidence including its limitations and uncertainties highlights areas for future research and helps medical practitioners better counsel and provide care to patients who may be experiencing or who have concerns about TSA/TSW.

Key Points

Topical steroid addiction and withdrawal encompasses the concept of dependence on topical steroids with worsening skin signs after its cessation. Skin manifestations may be more extensive or of a different morphology from the primary dermatosis.

Tachyphylaxis, dysregulation of glucocorticoid receptors, rebound vasodilation and impaired skin barrier leading to a cytokine cascade are plausible pathomechanisms, although evidence is insufficient.

1 Introduction

Topical corticosteroids (TCS) have a range of known side effects including skin atrophy, telangiectasia, tinea incognita and steroid rosacea (Table 1) [1, 2]. However, concepts such as topical steroid addiction (TSA) and topical steroid withdrawal (TSW) are controversial with majority of the dermatological community questioning this entity. Differences in opinion between dermatologists and patients who believe in TSA/TSW create challenges in treatment and a failure to acknowledge the patient's concerns can result in a weakening of the patient-healthcare relationship (ongoing study).

Concerns about TSA/TSW contribute to TCS phobia, which has a prevalence ranging from 21 to 83.7% [3]. Studies using the TOPICOP score[®] [4], a validated score to assess steroid phobia, have found an average score of between 40.3 and 44% (0 least fear, 100 most fear) [5–7]. Importantly, excessive TCS concerns can lead to excessive food restriction [8], use of harmful alternatives [9], and sub-optimal treatment [3], resulting in flares and escalation to systemic agents.

In 2015, the National Eczema Association (NEA) task force presented a systematic review including 1085 patients reported to have TSW [10]. Authors concluded that TSW is a distinct clinical event, but acknowledged that studies included were of “very low” quality. The review was updated

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Table 1 Local side effects of topical corticosteroid (TCS) and their proposed mechanisms

Local side effect	Proposed mechanism
Atrophy	Reduction in epidermal and dermal thickness through suppressive action on keratinocyte and fibroblast proliferation [32, 34, 44] and inhibition of collagen and lipid synthesis [64, 80]
Telangiectasia	Vasodilation via stimulation of dermal microvascular endothelial cells [81]
Purpura	Dermal atrophy and loss of intercellular substance causing blood vessels to lose the support of dermal matrix [82, 83]
Striae	Abnormal cross linking of collagen, reduction in dermal and connective tissue support [84, 85] that increases susceptibility to mechanical stretch [85, 86]
Hypopigmentation	Reduction in number and activity of melanocytes [87]
Delayed wound healing	TCS affects keratinocytes, fibroblasts, vascular connective tissue and angiogenesis [88]
Hypertrichosis	Stimulation of vellus hair growth by unknown mechanism [89]
Acneiform eruption, including steroid rosacea and perioral dermatitis	Not well understood. Proposed mechanisms include altered microbiome (e.g. an increase in demodex mites [90]) and degradation of follicular epithelium [91]
Cutaneous infections	Steroids mask the local immune response and falsely alludes to a clinical response while the infective organisms propagates (e.g. tinea incognita, Malassezia folliculitis) [92, 93]

in 2020 by Hwang and Lio and obtained consistent findings [11]. This present review aims to incorporate and evaluate what is known not just clinically, but also pathophysiologically about TSA/TSW through a comprehensive scoping of the literature. We searched PubMed, MEDLINE, Cochrane Library, Google Scholar, Embase and Web of Science to identify articles addressing TSA/TSW published from database inception to 16th June 2021. The following search terms were use “topical steroid”, “topical corticosteroid”, and “addiction”, “withdrawal”, “dependence”, “tachyphylaxis” and “rebound”. Hand searching of references of relevant articles was also performed. Information on definition, risk factors, clinical presentation, proposed pathogenesis, treatment and prognosis were extracted and summarised herein.

2 Definitions

The terms TSA and TSW appear to be used interchangeably without a clear diagnostic criteria or definition. Clinically, TSA/TSW has been described as a physical dependence on corticosteroids, with worsening of skin manifestations after withdrawal of TCS [10–14]. This rebound may be more extensive or with a different morphological appearance from the initial skin condition [15]. Some describe a decreasing effectiveness and an increase in quantity and potency of TCS required to control the skin condition [12, 16]. Psychological dependence may coexist, with resistance to stop despite awareness of its harmful consequences [13].

Other related terms include topical steroid damaged/dependent face (TSDF), red skin syndromes and red burning skin syndrome [12, 17–19]. TSDF was defined as the ‘semi-permanent or permanent damage to the skin of the

face precipitated by the irrational, indiscriminate, unsupervised, or prolonged use of TCS’, reported in the context of over-the-counter TCS containing lightening creams [18, 19]. Rapaport and Rapaport reported the “red skin syndromes”, described as a distinct patterns of chronic worsening eczematous rash including red face syndrome, post-peel syndrome, status cosmeticus, red scrotum syndrome, vulvodinia, perianal atrophoderma, chronic actinic dermatitis and chronic severe eczema [12, 17, 20].

While some authors include perioral dermatitis and steroid rosacea in their definitions of TSA/TSW [10, 14, 21] others consider these as being distinct [22].

3 Risk Factors for TSA/TSW

Studies that look at TSA/TSW in the context of predominantly inflammatory skin conditions indicate an that an equal number of males and females are at risk [16, 23], while those with mainly cosmetic use report a female majority [10, 11, 19].

The increased permeability of the stratum corneum is postulated as a risk factor [14, 24], with the face, and genital area having the highest percutaneous penetration [25] and thus being the most commonly affected sites [10, 11, 16]. The context for TCS use includes atopic dermatitis (AD) [10–12, 16, 26–28], cosmetic use and pigmentary disorders [10–12, 18, 19, 21], scrotal erythema [12], acne [10–12, 19, 28], rosacea [10, 28, 29] and perioral dermatitis [10]. Duration of TCS use ranged widely from 2 months to 40 years [11, 16, 21, 23], being typically of mid- to high-potency [10, 11, 16]. Longer periods of application and increased potency are believed to be risk factors for TSA/TSW [17, 28], with

a longer period of TCS use associated with greater rebound symptoms [7, 28].

4 Clinical Presentation of Patients Reported to have TSA/TSW

Clinical findings reported include oedema, vesiculation, prominent erythema, burning disproportionate to itch and erythema, and features of chronic steroid use such as telangiectasia, skin atrophy and acneiform papules resembling rosacea [11, 12, 16, 17, 26, 28, 30]. While such features are not specific, patients and authors have described these to be symptomatically and morphologically different from their primary dermatoses. Additionally, symptoms may be more severe with a questionnaire study reporting that 63.9% (529/828) of respondents had their most severe AD symptoms immediately after discontinuation of TCS [7]. Specific signs such as “red sleeve sign” and “elephant wrinkles” have also been described (Table 2). Following a systematic review, Hajar et al observed and reported 2 subtypes of patients with TSA/TSW; an erythematous subtype that occurred in patients with an underlying eczematous dermatosis, and a papulopustular subtype that occurred in patients who used TCS for a cosmetic or acneiform condition [10].

These are the phases of TCS withdrawal proposed based on previous observations [15, 31].

- I. An acute red exudative phase that starts typically a few days after cessation of TCS. This rebound eruption

extends to areas of the skin where TCS have never been applied [14, 15, 17].

- II. A dry itchy desquamative phase ensues.
- III. A recovery phase where the skin shows gradual improvement but is “sensitive” to minute stimuli. Periods of aggravation and flares may occur intermittently [17]. Sensitivity decreases over time.
- IV. A recovered phase where the skin returns to its original appearance, which may be completely healthy or that of the original skin condition (e.g., in AD). The entire process of recovery may take weeks to years [15].

5 Differentials

Prior to the diagnosis of TSA/TSW, patients were often given alternate diagnosis including worsening of the underlying dermatitis, allergic contact dermatitis, rosacea and systemic lupus erythematosus (due to facial redness) [12].

6 Pathogenesis

Topical corticosteroids work at the cellular level via genomic and non-genomic pathways to achieve anti-inflammatory, antiproliferative, immunosuppressive and vasoconstrictive effects [32–35]. The genomic pathway refers to the actions of the glucocorticoid receptor and its subsequent transcriptions of genes with anti-inflammatory functions and downregulation of pro-inflammatory genes. The non-genomic pathway is responsible for the rapid effect of TCS by affecting target

Table 2 Reported signs and symptoms of TSA/TSW

Erythema

Widespread. May involve areas distant from original site of dermatitis or sites where TCS were never applied [12, 15, 17, 23, 66]

Oedema, exudation and oozing [12, 14, 23, 66, 68]

Burning or pain [12, 17, 23, 66]

Itching [12, 16, 23, 26, 66, 68]

Pustulation or Acneiform lesions [12, 30]

Vesiculation [12, 66]

Desquamation and skin shedding [23, 26, 66]

Lymphadenopathy [23, 66]

Red sleeve sign

Erythematous rash ending abruptly at the dorsal and palmar border, sparing the palms and soles [11, 15, 16, 23, 66]

Headlight sign

Eruption over the face, sparing of the nose and the upper lip [11, 16, 17, 66]

Elephant wrinkles

Thickened skin with reduction in skin elasticity, usually on the extensors [11, 16, 23]

These findings are reported from clinical observations, and objective differentiation from the primary dermatoses is challenging
TCS topical corticosteroid, TSA topical steroid addiction, TSW topical steroid withdrawal

cells such as monocytes, T cells and platelets without the use of protein synthesis.

Particular mention should be made of steroid-induced atrophy as this is a common concern. Steroid-induced atrophy results from inhibition of cell proliferation and collagen synthesis (Table 1) [36, 37]. This is dependent on the duration of use [38], potency [39], and anatomical area treated [2, 40]. Although the degree of steroid-induced atrophy is proportionate to the above factors, previous studies suggest that skin thickness returns to normal values in approximately 2 weeks following discontinuation of TCS treatment. However, these studies were conducted in patients with normal skin and short periods of TCS use, which may not translate to real-world conditions in patients with chronic inflammatory skin disorders [38, 41, 42].

7 Postulated Mechanisms for TSA/TSW

7.1 Tachyphylaxis

Tachyphylaxis, the decreasing effect of TCS when applied continuously, has been shown in small studies [43–46]. In 1976, du Vivier et al. showed that the initial three to five applications of TCS to mouse skin resulted in inhibition of DNA synthesis, but DNA synthesis increased after 7 applications before returning to normal with 13 applications [44]. Both twice-daily and alternate-day application of TCS resulted in this same pattern but was less marked in the alternate-day group [43]. A decrease in vasoconstrictive response [45] and histamine-induced wheal suppression [46] have also been reported with repeated TCS applications. These suggest that continued TCS application may result in insensitivity to its anti-proliferative, vasoconstrictive and histamine suppressive effects.

Interestingly, TSA/TSW is rarely reported in psoriasis patients and further research and comparison between psoriasis and atopic dermatitis may shed greater understanding of the pathogenesis of TSA/TSW.

7.2 Dysregulation of Glucocorticoid Receptor

The therapeutic action of glucocorticoids occurs through binding to the intracellular glucocorticoid receptor (GR) and mineralocorticoid receptor (MR) [47, 48], mediating the transcription of pro-inflammatory genes and regulating epidermal proliferation and differentiation [47, 49].

Early cell models studies showed that exposure to glucocorticoids resulted in down-regulation of GR DNA and mRNA [50, 51]. Subsequent studies have gone further to study variations in the two splicing variants of GR, the GR α and GR β isoform [52, 53]. In 2009, Hagg [52] observed that following TCS treatment, patients with poor clinical

response had upregulated GR β expression while this was unchanged in patients with good clinical response. Authors postulated that the increased expression of GR β correlated with glucocorticoid insensitivity in atopic dermatitis. Further studies are required to confirm the association between expression of GR and its isoforms and steroid responsiveness.

7.3 Dysregulation of Cortisol Production by Keratinocytes

In 2016, Fukaya postulated that TSA/TSW was due to suppressed production of cortisol in keratinocytes after TCS use [54]. He stained skin biopsy specimens from 8 patients with atopic dermatitis and 1 healthy control with anti-cortisol antibody. In patients with rebound phenomenon after stopping TCS, the cortisol pattern in the epidermis had a patchy staining of anti-cortisol antibody, compared to a homogenous staining in healthy patients or those recovered from TSA/TSW. He hypothesised that TCS application causes a decrease in self-production of cortisol by keratinocytes. However, a second study by Fukaya in 2017 showed an increase in cortisol staining in the epidermis with TCS application, followed by a decrease after cessation in a single healthy volunteer after 2 weeks of clobetasol propionate application [53]. The evidence for this thus remains unclear.

7.4 Rebound Vasodilation

The clinical efficacy and potency of the TCS is correlated with the degree of vasoconstriction it induces [2, 55]. This is mediated through suppressed production of vasodilators like nitric oxide (NO), histamine, and mediators of vascular smooth muscle reactivity [35, 56].

A study of 12 patients with red scrotum syndrome reported predominant features of burning, pain and bright erythematous skin together with ectatic venules in 4 out of 7 patients on histology [24]. This led the authors to propose a vasodilatory and neurovascular mechanism for TSA/TSW.

Rapaport and Rapaport [12, 57] postulated that the erythema and burning seen in TSA/TSW is caused by rebound vasodilation mediated by NO. A group of 38 patients with TSA had their serum NO compared against controls who had either recovered from TSA/TSW or had mild eczema. Patients with TSA/TSW had a statistically higher mean NO level compared to the control group and most showed a temporal decrease in serum NO levels after TCS cessation (without details on clinical improvement). However, the study was unable to demonstrate a temporal relation between elevated NO level and the presence of the flare and it is unclear if the level of elevation of serum NO in the TSA/TSW group could account for the clinical signs.

Previous studies have also shown that inflammatory skin diseases such as atopic dermatitis are associated with higher levels of serum NO [58, 59]. Thus, it cannot be concluded if the elevated NO is related to TSA/TSW or the underlying inflammatory skin condition. Finally, NO seems to exhibit both anti- or pro-inflammatory effects [60–62] depending on its concentration and microenvironment, with studies showing beneficial anti-inflammatory effects of topical NO-releasing compounds [62, 63]. Further investigation into the relationship between NO levels, disease course and treatment will be helpful.

7.5 Rebound Cytokine Cascade Secondary to TCS Induced Barrier Impairment

TCS use has been shown to result in barrier dysfunction [37, 44, 64]. In a hairless mouse model study, Lin et al [37] found that cessation of 0.064 % betamethasone dipropionate ointment after a 6-week use led to an increase in transepidermal water loss (TEWL), higher expression of Ki-67 (a cell proliferative marker) and upregulation of IL1- α , TNF- α and NF- κ B. These cytokines gradually normalised after 1 week. Authors proposed that the barrier disruption from TCS use induces a cytokine cascade once the anti-inflammatory effects of TCS are withdrawn, manifesting in a withdrawal dermatitis. Interestingly, concurrent application of petrolatum during TCS use had attenuated the barrier impairment and cytokine production suggesting the importance of concurrent moisturisers.

8 Investigations

A patch test is useful in excluding an allergic contact dermatitis to TCS [12], although challenges include the lack of normal skin for patch testing, false negative results due to delayed reactions and false positive due to vasodilation [12, 65]. Skin histology of patients with TSA/TSW is non-specific, with epidermal atrophy [31], spongiosis [12, 16], and parakeratosis described [16].

9 Treatment

Treatment recommended by various authors primarily involves tapering [14] or complete cessation of TCS [12, 15]. The rationale proposed for an immediate cessation without a taper is that the vasoconstrictive properties of TCS contributing to TSA/TSW would still remain despite a lower potency [12].

General measures recommended during the withdrawal phase include lifestyle modifications such as dietary changes and stress control [12], psychological support [12, 15, 18],

cold water and ice [12, 66], systemic antibiotics and astringents to prevent and treat concomitant bacterial infection [12, 15], analgesics [12] sedatives [12] antihistamines [66], anxiolytics [12], and oatmeal-containing bath products [12]. Other treatments tried include topical calcineurin inhibitors [67], crisaborole [67], phototherapy [67], cyclosporin [12, 67], and dupilumab [67]. Acneiform eruptions like steroid rosacea and perioral dermatitis can be treated with oral antibiotics such as doxycycline [66]. Response to therapy was inconsistent and studies were low quality, being limited to case reports or small series and thus cannot be used to generate recommendations for treatment.

10 Prognosis

Complete cure and resolution were reported to have occurred between weeks to years [10, 12, 15, 23, 26]. However, there is considerable variability in persistence of outcomes. Cessation of TCS in 24 atopic dermatitis patients with concerns of TSW led to improvements in symptom severity and DLQI scores over 2 years [26]. A study by Juhász et al from California, which reviewed blogs of children with reported TSA/TSW reported that 7 of 13 subjects continued to have “active TSA/TSW symptoms such as shedding, oozing, erythema, pain and itching” even 20 months after cessation of TCS [23]. A survey of 3840 participants with self-reported TSA/TSW found that 26% of those who had stopped TCS for greater than 5 years reported persistence of symptoms [68].

11 Discussion

Is there a basis for steroid phobia? Current evidence for TSA/TSW is insufficient and at points contradictory. Furthermore, majority of the studies are of low quality and at high risk of bias. Certain authors describe distinct clinical presentations of TSA/TSW; however, there is no consensus on a diagnostic criterion or the patterns of associated TCS use that result in TSA/TSW. It also remains difficult to concretely establish a difference between TSA/TSW and a flare of the pre-existing inflammatory skin diseases. Additionally, experimental studies of short TCS application in healthy volunteers may not be generalisable to dermatological patients with chronic TCS use. Despite these limitations, we believe it is still rational to entertain the possibility of TSA/TSW, given the non-conclusive nature of existing research and the mechanistic potential of tolerance, withdrawal and rebound reported with other medications such as intranasal vasoconstrictors [69], benzodiazepines [70], histamine-2 receptor blockers [71], antidepressants [72] and oral steroids [73].

Although TSA/TSW is a controversial entity in the medical community, there are online communities of patients who

report experiencing TSA/TSW. Medical professionals who fail to acknowledge the concerns of this group risk being viewed as dismissive and many patients will instead seek alternative treatments including those from online support groups (ongoing study). Various medical and dermatological groups now have public facing pages acknowledging the entity of TSA/TSW. For example, the British Association of Dermatologists and National Eczema Society recently published a joint position statement on TSA/TSW in January 2021, tactfully addressing TSA/TSW without comment on its validity [74].

Further research into TCS use in groups without an underlying primary inflammatory skin disorder, varying potencies and durations of TCS use, and longitudinal studies with a control arm would be important. A multi-omic analytic approach (e.g., metabolomics, microbiomics, proteomics and lipidomics) may help in further delineating the difference between TSA/TSW and the underlying primary inflammatory skin disorder. Concurrently, the development and evaluation of different TCS formulations and application regimes [75] may result in fewer side effects, systemic absorption and skin atrophogenicity [76, 77]. Non-steroidal topical therapies [78, 79] will help to provide alternate options for patients who wish to avoid or reduce the side effects of TCS. Finally, engagement of patient support groups by the medical community and an open and objective discourse about TSW/TSW is needed to foster mutual respect and trust.

12 Conclusion

TCS are useful for many patients who suffer from inflammatory skin diseases. The challenge for dermatologists is in deciding treatment potency and duration to obtain the greatest benefits with the least number of side effects. In scientifically reviewing the clinical presentations and postulated mechanisms surrounding this controversial topic of TSA/TSW, medical practitioners and patients may better approach the use or non-use of TCS with greater objectivity and awareness.

Declarations

Author Contributions EC, ST, NSC conceived the review idea. EC and NSC performed the search and EC and ST filtered the articles for inclusion. All authors reviewed the included manuscripts and contributed equally to the drafting and review of the manuscript.

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