NEWS, VIEWS, & REVIEWS

Practical Approaches to the Diagnosis and Management of Sensitive Skin: A Scoping Review

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Introduction

Sensitive skin (SS), a subjective syndrome of cutaneous hyperreactivity to otherwise innocuous stimuli, affects approximately 40-50% of the population. Increased stratum corneum permeability, hyperactivity of intraepidermal nerve fibers, and sensitization of transient receptor potential vanilloid 1 (TRPV1) channels contribute to the lower sensitivity threshold and neurosensory discomfort of SS, however, pathophysiology is incompletely understood.[1,2] SS manifests as dry, easily irritated skin (commonly on the face) with reactive erythema, pruritis, burning, tightness, or stinging. There is limited data on SS management to guide clinical decision-making and no consensus on best approach. Despite these challenges, dermatologists should be equipped to encounter SS; individuals with SS are more likely seek dermatology care and more likely to rely on medical advice for skincare product purchases than those without SS.[3] Herein, we present a practical approach to the patient with SS and briefly highlight novel treatments using current evidence in the literature.

SS should be considered a diagnosis of exclusion; other dermatoses that increase skin sensitivity (Table 1) must be identified and appropriately treated if present. Patients initially presenting with SS should discontinue all topical products for two weeks, then undergo dermatologic evaluation. If SS is still suspected, products can be gradually tested and reintroduced with emphasis on identifying triggers for reactivity. SS may be triggered by lifestyle-related (cosmetics, products, foods, alcohol), environmental (pollution, UV exposure, heat, weather), or endogenous (psychological factors, hormonal changes, stress) factors.[1] Patients should develop a list of triggers and minimize exposures.[4,5] Sensitive Scale-10 (SS-10), a validated scale measuring severity of SS,[6] can be used to establish a baseline and track symptoms longitudinally.

Table 1. Differential Diagnosis for Sensitive Skin

Differential Diagnosis for Sensitive Skin
Eczema/Atopic Dermatitis
Rosacea
Seborrheic Dermatitis
Irritant or Allergic Contact Dermatitis
Photodermatoses
Urticaria
Acne
Xerosis

During acute periods of SS reactivity, severe neurosensory discomfort can be managed with topical calcineurin inhibitors (TCIs). TCIs' anti-inflammatory and anti-pruritic effects occur through inhibition of calcineurin-dependent T-cell activation, reducing pro-inflammatory cytokines. Calcineurin inhibition also paradoxically favors activation of TRPV1, a channel perpetuating neurogenic inflammation.[7] This explains the initial irritating effect of TCI application, while eventual channel desensitization allows for soothing effects of prolonged use.[8] SS, associated with TRPV1 sensitization, benefits from this long-term mechanism; application of pimecrolimus 1% cream significantly reduces pruritis and burning sensations in SS patients.[9]

Long-term management of SS necessitates daily skincare that improves skin hydration, increases stratum corneum integrity, and decreases susceptibility to irritants.[10-12] Fundamental SS skincare routines include mild cleanser, moisturizer, and sun protection.[13] Preferred cleansers have a pH near physiological skin and contain emollients. Patients should avoid facial washing with water or soap to limit excessive removal of lipids and natural moisturizing factors.[14] Optimal moisturizers contain humectants (eg: glycerin, hyaluronic acid, aloe vera) and emollients (ceramides, plant oils).[1] Lastly, daily sunscreen should be broad-spectrum, SPF 30 or greater, and include inorganic UV filters (titanium dioxide, zinc oxide) due to lower allergenic potential.[11] All formulations should be fragrance-free, hypoallergenic, and non-irritating.

Active ingredients in skincare products can be tailored to target symptoms of SS. There is currently no federal or legal standard regulating ingredients in products marketed for SS,[15] and many lack testing in SS specifically. Therefore, understanding of the specific active ingredients in sensitive skincare and their utility in related conditions can aid product counseling. We review the evidence for common active ingredients in SS products in Table 2. The best products will likely involve a synergistic effect of several ingredients.

Table 1. Current Evidence on Common Active Ingredients Found in Sensitive Skin (SS) Products.

	Active Ingredient	Purpose	Mechanism	Relevant Evidence	Potential Utility in SS
	Niacinamide[22] *aka nicotinamide*	Involved in energy production as component of coenzymes NAD and NADP, which serve as antioxidants in their reduced forms (NADH/ NADPH)	Decreases pro-inflammatory NF- κβ signaling by inhibiting PARP- 1 Reduces pruritis by inhibiting cAMP-phosphodiesterase, which is involved in mast cell histamine release	Increases synthesis of ceramides, free fatty acids, and cholesterol *in vitro* Topical application reduced TEWL in a clinical study (n=12)	Topical application may improve barrier function
Peptides	Acetyl dipeptide- 1 cetyl ester[22]	Synthetic ligand developed to reduce stinging sensation and inflammation from skin exposure to irritants	Promotes pro-opiomelanocortin gene expression, which stimulates release of opioid metenkephalin and reduces CGRP release (which otherwise activates TRPV1)	Reduced PGE2 secretion and NF- κβ signaling *in vitro* Upregulated Aquaporin 2, Filaggrin genes *in vitro* (promote epidermal barrier) 2 clinical studies from manufacturer brochures report increased skin comfort and decreased heat sensations after use	Expected to help mitigate unpleasant sensations associated with hyperactivity of cutaneous nerve fibers
	Panthenol/ Pantothenic Acid[22]	Pantothenic acid (biologically active, Vitamin B5), helps comprise coenzyme A (CoA)	CoA is essential for metabolic processes including synthesis of epidermal intercellular lipids	Moisturized and improved skin barrier in RCT of AD patients Promotes wound healing in multiple clinical studies, thought to be due to fibroblast activation	Expected to improve skin barrier
	Palmitoyl tripeptide- 8[22]	Synthetic peptide based on α- melanocyte-stimulating hormone	Downstream effects of include reduction of NF- κβ signaling and reduced inflammatory response	Demonstrated improvement in erythema, dryness, edema, and stinging in a clinical study of rosacea patients	Symptom reduction in rosacea should translate to SS given symptom overlap
	Ceramides[10,14,23–25]	Major component of lipid-enriched intercellular matrix in stratum corneum (also contains free fatty acids and cholesterol)	Essential role in providing and maintaining barrier function of epidermis	Ceramides are relatively decreased in the stratum corneum of SS patients Lipidome analysis in SS demonstrated decreased levels of ceramides More effective than standard emollients for improving skin hydration and inflammation in AD	Essential for barrier function Demonstrated lack of ceramides in SS

Other ingredients reported in literature to have potential utility in SS include glycyrrhetinic acid (and derivatives),[22,26] 4- t- butylcyclohexanol[22,27–29] allantoin,[22] *Laminaria ochroleuca*,[22] *Centella Asiatica* (Gotu kola),[22] bakuchiol,[30] *Bifidobacterium longum* extract,[31] coriander[32] and flax seed oil[33] supplementation, *R. rosea* extract,[34] Grifolin derivatives (*Albatrellus ovinus*),[35] neurosensine[36]

TEWL= transepidermal water loss, AD = atopic dermatitis

Beyond the above approaches, phototherapy has been investigated in SS given demonstrated anti-inflammatory effects in other conditions.[16,17] In one study, red light emitting diode (LED) exposure twice weekly allowed 77% of participants (n=30) to achieve significant SS-10 score reduction within 6 or fewer sessions.[17] Interestingly, SS-10 scores remained decreased at 2 month follow-up from the final session, suggesting benefits may persist beyond the final treatment.[17] Other studies demonstrated successful SS symptom reduction using low-level light therapy,[18] intense pulsed light (IPL) alone[16], and in IPL combination with shortwave radiofrequency.[19] Phototherapy shows promise as an intensive SS therapy, but additional evidence is needed to determine the most advantageous regimen.

Novel approaches to SS include extracellular vesicles extracted from mesenchymal stem/stromal cells, which were tested in 22 SS patients. This therapy (1mL application BID for 28 days) improved objective and subjective SS symptoms and reduced reactions to chemical irritation.[20] Plasma rich in growth factors (PGRF) was studied in 5 SS patients; personalized PGRF serums were prepared from peripheral blood and applied to the face twice daily for 3 months. Results included increased skin hydration and decreased objective symptoms of SS.[21] Although there were no adverse effects reported in these studies, they are likely not feasible for widespread use.

In conclusion, SS management is highly personalized and relies on strong patient-physician partnership and a high level of patient involvement to achieve relief of symptoms, optimize skincare, and identify triggers. There is a need for affordable, efficacious, and scientifically-tested therapeutics for SS. Currently, an overall paucity of literature on SS management and heterogenous methods for diagnosis and outcome-tracking make it difficult to gauge comparative efficacy of therapeutic options. We intended to simplify current evidence and highlight relevant data applicable to clinical practice. We hope that future research can explore SS pathophysiology, therapeutic targets, and product evaluation in SS patients.

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