Skin-Lightening Agents: An Overview of Prescription, Office-Dispensed, and Over-the-counter Products

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Not so long ago, there was a limited number of skin-lightening agents, with hydroquinone (HQ) being the most efficacious. Currently, there are a plethora of agents, some as effective as HQ; some are available over-the-counter (OTC) and others are physician dispensed. The purpose of this article is to provide physicians with an overview of available skin brighteners, including HQ, mequinol, topical retinoids, azelaic acid, arbutin and deoxyarbutin, kojic acid, licorice extract, ascorbic acid, soy, aleosin, niacinamide, and *N*-acetylglucosamine.

Pigmentation disorders can be an issue for all individuals, especially those with skin of color.[1,2] Although the natural pigmentation in patients with skin of color provides many advantages such as sun protection and slowed signs of aging, it also increases susceptibility to hyperpigmentation, which can have a negative psychological impact. A study assessing the most common diagnoses in patients of various racial and ethnic groups treated at a hospital-based dermatology faculty practice revealed that dyschromia was among the 5 most common diagnoses observed,[3] providing evidence that hyperpigmentation is a major concern for darker-skinned racial ethnic groups.

Dermatologists and patients have a number of options when treating hyperpigmentation. Although some patients may use prescription medications from dermatologists, others seek assistance from over-the-counter (OTC) agents manufactured in the Unites States or abroad. Dermatologists face the following challenges: (1) how does one become familiar with the many OTC agents that are available to patients, and (2) how does the accessibility to such products impact the treatment regimen tailored by dermatologists? This review aims to provide physicians with an overview of prescription agents, office-dispensed and OTC agents that patients use for self-medicating, complications of long-term use, and recommendations for management.

PRESCRIPTION MEDICATIONS FOR HYPERPIGMENTATION

The most common indications for skin-lightening agents include postinflammatory hyperpigmentation (PIH) and

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melasma. Other uses by some patients include general skin lightening, or skin brightening. Prescription active ingredients used for pigment skin lightening are hydroquinone (HQ), mequinol, topical retinoids, and azelaic acid.[4]

Hydroquinone

Hydroquinone, the gold standard in the treatment of hyperpigmentation for more than 50 years, is a phenolic compound that reduces the conversion of dihydroxyphenylalanine to melanin by inhibiting tyrosinase,[5] possibly by binding to the enzyme or by interaction with copper molecules at the enzyme's active site.[6] This inhibition leads to distorted melanosome formation, increased melanosome destruction, and inhibition of DNA and RNA synthesis. Hydroquinone has been extensively researched and proven efficacious in treating hyperpigmentation. It is available in a 2% concentration in OTC formulations and 3% to 4% concentrations in prescription formulations. Good to excellent responses have been reported with 2% HQ preparations in 14% to 70% of 12 treated patients.[7] Hydroquinone concentrations of 3% to 5% are more effective, but irritant dermatitis may occur.[5] Table 1 lists some prescription medications containing 4% HQ.

Making HQ into a stable preparation is challenging because of the highly reactive oxidative nature of the agent, changing from creamy white to a darker yellow or brown via oxidation. Efficacy diminishes as the discoloration progresses; thus products with off-color change should be immediately discarded.[4] In an attempt to increase the skin-lightening potency of prescription formulations, some products include penetration enhancers such as glycolic acid or tretinoin to supplement the pigment-lightening effect. The addition of microsponges enhances the timed delivery of HQ to the skin, while the addition of sunscreen ingredients prevents UV-induced pigment darkening.

The impetus to find other agents for the treatment of hyperpigmentation arose out of controversy surrounding the safety of topical agents containing HQ. In 2006, the US Food and Drug Administration did not receive the collaborative studies on the safety of HQ as requested from the pharmaceutical industry and consequently stated it would withdraw all 2% OTC HQ preparations and prescription formulations that were not studied as investigational new drugs (thus excluding Tri-Luma [Galderma Laboratories, LP]) once currently manufactured supplies were depleted.[8] The final ruling by the US Food and Drug Administration is still pending.

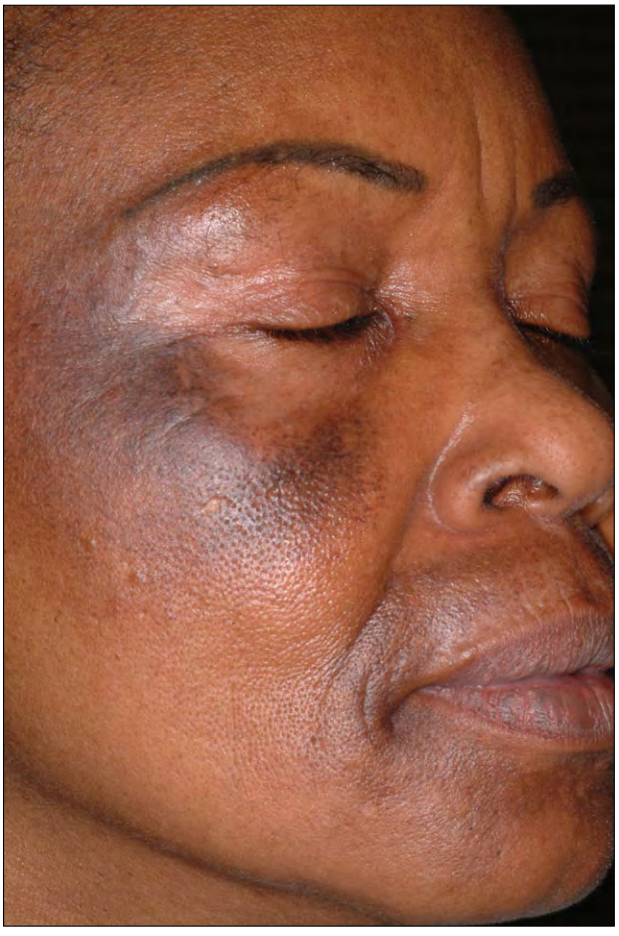
Sheth and Pandya[6] discussed the growing concern of the use of topical OTC HQ preparations, stating that this apprehension exists largely because of the perceived risks

TABLE 1

Select Medications Containing 4% Hydroquinone

Product Name	Manufacturer	Active Ingredient(s)	Office Dispensed[a]
Aclaro PD	Innocutis	HQ 4%	Yes
Blanche	Neocutis	HQ 4%	Yes
Glytone Clarifying Cream	Pierre Fabre Dermo-Cosmetique	HQ 4%	Yes
Glytone Clarifying Gel	Pierre Fabre Dermo-Cosmetique	HQ 4%	Yes
Hydro Q	DermAvance Pharmaceuticals Inc	HQ 4%	Yes
Lustra	Taro Pharmaceuticals Inc	HQ 4% + GA	No
Lustra-AF	Taro Pharmaceuticals Inc	HQ 4% + GA + sunscreen	No
Lustra-Ultra	Taro Pharmaceuticals Inc	HQ 4% + retinol	No
Nu-Derm Blender	Obagi Medical Products, Inc	HQ 4%	Yes
Nu-Derm Clear	Obagi Medical Products, Inc	HQ 4%	Yes
Tri-Luma	Galderma Laboratories, LP	HQ 4% + tretinoin 0.05% + FA 0.01%	No

Abbreviations: HQ, hydroquinone; GA, glycolic acid; FA, fluocinolone acetonide.
[a]Not in all states.



Exogenous ochronosis from long-term use of hydroquinone therapy.

of therapy and the need for clinical data supporting the approval of currently marketed products. Exogenous ochronosis, characterized by asymptomatic hyperpigmentation, erythema, papules, papulonodules, and gray-blue colloid milia on sun-exposed areas of the skin,[5] has been reported in the literature (Figure). This condition has been linked to the use of HQ and may not be caused by the concentration of HQ in the product but rather the extended use of the agent.[9] Its occurrence after HQ use is remarkably less common in the United States than in African countries. One plausible explanation is that the agent can be obtained OTC in concentrations of up to 8% in other countries. Easy accessibility to high concentrations of HQ can lead to overuse and increased risk for adverse events. Additionally, Olumide et al[10] reported that such OTC preparations may contain various additives thought to enhance the bleaching effect, such as resorcinol, mercury, lemon juice, potash, toothpaste, liquid milk, crushed camphor balls, ascorbic acid, peroxides, and chlorates that may contribute to the development of exogenous ochronosis. Other long-term complications include nail discoloration, conjunctival melanosis, and corneal degeneration.[11]

There is controversy about the safety of HQ and its association with malignancies. There are several articles that address this specific issue.[12-17] There are human case reports implicating HQ as a cause of leukemia. Three cases of chronic occupational exposure to radiographic developing solutions containing HQ have been reported.[15,16] A 2012 case report described a male with a 16-year occupational exposure to radiographic developing solution (25 g/L) with no other risk factors for leukemia who developed chemically induced myelodysplasia and acute myeloid leukemia.[15] The other report is of 2 Greek female radiation technologists, also with a 16-year history of occupational exposure to HQ, who developed acute myeloid leukemia. The authors hypothesized that the chemically induced leukemia originated from exposure to HQ and/or glutaraldehyde.[16] Another case from Pakistan described a patient who developed pseudolymphoma 1 month after he used topical HQ 4% for melasma.[18] Finally, squamous cell carcinoma has been reported in 2 black women with Fitzpatrick skin type VI who used bleaching compounds for several years. It is unclear at this point if HQ, cortisone-induced immunosuppression, or another compound was responsible for the carcinogenesis.[17]

In contrast, HQ is found in various foods and no retrospective case series, prospective trial, or epidemiologic study in the United States has revealed a case of malignancy induced by HQ.[12-14] Hydroquinone is found at various concentrations in coffee, tea, wheat cereal, and pears. In an example examining the bioavailability and blood levels of topical versus food-derived HQ, one author offered the analogy that applying 0.5 g of HQ cream 4% in a 12-hour period was "no more dangerous than eating a pear with its skin, a bowl of wheat germ, and a cup of coffee."[12] A 16-year epidemiologic study of almost 500 photographic processors "showed no significant excess mortality, sickness-absence, or cancer incidence."[13]

Mequinol

A derivative of HQ, mequinol (4-hydroxyanisole) is typically formulated with tretinoin. It is a phenolic agent that acts as a competitive inhibitor of tyrosinase without damaging melanocytes, as its parent compound does.[6] Mequinol is approved for use in the United States and Europe in a 2% concentration and is sold as a prescription pigment lightener in combination with tretinoin 0.01% and vitamin C to enhance penetration and skin lightening, respectively.[19-23]

Fleischer et al[20] reported that mequinol is effective in improving the appearance of solar lentigines and other

hyperpigmented lesions in a 2% formulation in combination with tretinoin 0.01%. Although mequinol has been reported to cause long-standing depigmentation in some white patients, repigmentation typically occurs with time. This agent in combination with tretinoin may lead to PIH in some black patients; however, the hyperpigmentation lightens over time once the topical medication is discontinued.[22,24,25]

Topical Retinoids

The prescription topical retinoids used for improvement in skin pigmentation are tretinoin, adapalene, and tazarotene. Tretinoin (retinoic acid) increases keratinocyte proliferation and epidermal cell turnover by impairing glutathione-dependent cytoprotection via inhibition of glutathione S-transferase, which results in accentuation of melanin loss from the epidermis and also potentiates the depigmenting effects of other agents, but tretinoin does not directly suppress melanogenesis.[26,27] Concentrations range from 0.01% to 0.1%, though irritant contact dermatitis is a common side effect with higher concentrations. Tretinoin is sometimes used to treat hyperpigmentation but typically requires months to show improvement.[28]

Adapalene is a viable alternative for patients unable to tolerate tretinoin.[6] It is a synthetic retinoid with greater selectivity than tretinoin for the β- and γ-retinoic acid receptors but not the α-retinoic acid receptors. Jacyk and Mpofu[29] evaluated the efficacy and safety of adapalene gel 0.1% in a 12-week open-label study of 65 African patients, demonstrating significant improvement in the degree of PIH at weeks 4, 8, and 12 compared with baseline ($P<.01$). Moderate or severe skin irritation was reported in less than 5% of patients during treatment.[29] In a different study, another synthetic retinoid, tazarotene cream 0.1%, was reported to significantly reduce overall disease severity, intensity, and hyperpigmentation within 18 weeks compared with vehicle ($P\leq.05$).[30]

Azelaic Acid

The irritation profile of HQ and retinoids was the impetus to discover other pigment-lightening ingredients in the prescription realm. Azelaic acid is a naturally occurring dicarboxylic acid obtained from cultures of *Malassezia furfur* (also known as *Pityrosporum orbiculare*). It acts by inhibiting tyrosinase activity, DNA synthesis, and mitochondrial enzymes, thus blocking direct cytotoxic effects toward melanocytes. Originally developed for treatment of acne and rosacea, azelaic acid is now used for the treatment of PIH.[31,32] It is currently available as a gel in a 15% concentration in the United States. Because of its selective affinity for abnormal melanocytes, azelaic acid has no depigmenting effects on normally pigmented skin.

In a 24-week double-blind trial comparing azelaic acid cream 20% to HQ cream 4%, azelaic acid was shown to be equally as efficacious as HQ cream 4%.[32] Azelaic acid has an excellent safety profile but may cause short-lived stinging in some patients. The most commonly reported side effects include pruritus, mild erythema, scaling, and burning. Azelaic acid has been shown to be safe and efficacious in formulations with retinoids and glycolic acid.[33,34] Other alternative combinations include the use of topical potent corticosteroids, such as clobetasol propionate, with azelaic acid cream 20%, as demonstrated by Sarkar et al.[35]

Combination Agents

The Kligman-Willis formula was one of the first combination topical therapies developed for the treatment of hyperpigmentation, consisting of HQ 5%, tretinoin 0.1%, and dexamethasone 0.1%.[36] In this combination product, HQ and tretinoin lighten the skin; tretinoin attenuates the oxidation of HQ and aids epidermal penetration; and dexamethasone decreases irritation from the first 2 ingredients, reduces cellular metabolism, and prevents melanin synthesis.[6] Approximately 3 weeks of twice-daily use is required to observe improvement. Studies also have shown that incorporation of a potent topical corticosteroid helps prevent excess irritation, which had previously led to decreased patient compliance and/or PIH.[36-38]

Dual-combination topicals that have been tested include HQ plus retinoic acid and HQ plus retinol. Studies have shown that concomitant use of daily photoprotection of at least sun protection factor (SPF) 15 substantially increased the efficacy of topical therapy.[39,40]

One of the most efficacious triple-combination formulations for the treatment of melasma has been HQ 4%, tretinoin 0.05%, and fluocinolone acetonide 0.01%, in conjunction with regular use of photoprotection with an SPF 30 sunscreen. One study found that 26.1% of patients using triple-combination treatment (n=161) achieved complete clearance after 8 weeks versus the 3 dual-combination formulations (9.5% for HQ plus tretinoin [n=158]; 1.9% for tretinoin plus fluocinolone [n=161]; 2.5% for HQ plus fluocinolone [n=161]).[41] Seventy-seven percent of patients using the triple-combination agent achieved complete or near-complete clearance versus a maximum of 46.8% of patients using a dual-combination regimen. Adverse events occurred in the majority of patients and included erythema, desquamation, burning, dryness, and pruritus, with the severity rated as mild for most.[41] Because irritation may lead to the development of PIH in patients with darker skin types, decreased usage can be employed.

NONPRESCRIPTION OFFICE-DISPENSED AND OTC AGENTS

Nonhydroquinone-active agents also can be used for pigment lightening in office-dispensed and OTC preparations. Table 2 lists some OTC and office-dispensed skin-lightening products.

Retinol and Derivatives

Although skin lightening is more remarkable with prescription retinoids, OTC retinol provides similar efficacy. Retinol is the dietary form of vitamin A with a lower potency than retinoic acid (tretinoin); it induces changes in skin similar to tretinoin but with minimal irritation. Not nearly as effective in pigment lightening, retinol is required in 10-fold higher concentrations to produce epidermal effects similar to retinoic acid. Retinol is unstable in higher concentrations, posing a challenge in creating stabilized formulations.

A 12-week trial comparing tretinoin cream 0.025% and tri-retinol cream 1.1% (retinol, retinyl acetate, and retinyl palmitate) in 34 women with Fitzpatrick skin types I to IV found no statistical difference in photodamaged skin (photodamage overall, $P<.01$; mottled pigmentation, $P<.001$).[42]

Arbutin and Deoxyarbutin

The most effective OTC pigment-lightening agents are botanicals that are structurally similar to HQ.[4] Arbutin, a naturally occurring β-D-glucopyranoside, causes decreased tyrosinase activity without affecting messenger RNA expression, while also inhibiting melanosome maturation without being toxic to melanocytes.[43,44] It is derived from the bearberry plant (*Arctostaphylos uva-ursi*) and in lesser amounts from cranberry and blueberry leaves. Arbutin is a component of a myriad of cosmeceutical lightening formulations marketed in the United States and is used in various preparations in Japan at 3% concentrations.[5] Higher concentrations are more efficacious but may cause a paradoxical pigment darkening from PIH. The synthetic deoxyarbutin is a more potent tyrosinase inhibitor and has been shown to be more effective more rapidly, possibly distinguishing it as the most effective OTC lightening agent.[4,45] Research has demonstrated that the deoxyarbutin-induced skin lightening of solar

Table 2

Select Over-the-counter and Office-Dispensed Skin-Lightening Agents

Product Name	Manufacturer	Active Ingredient(s)
Aveeno Positively Radiant	Johnson & Johnson Consumer Companies, Inc	Soy
Elure	Syneron Medical Ltd	Melanozyme: lignin peroxidase
Lumixyl	Envy Medical	Decapeptide-12
Lytera	SkinMedica	Retinol, TA, linoleic acid, glabridin, HR, niacinamide, 4-EB
Mela-D Pigment Control	La Roche-Posay Laboratoire Dermatologique	LHA, GA, kojic acid
Olay Total Effects Tone Correcting	Procter & Gamble	*N*-acetylglucosamine
Perle	Neocutis	Melaplex: DG, leucine, PR, UP
Pigment Regulator	SkinCeuticals	Emblica, kojic acid, exfoliants
Professional-C Serums	Obagi Medical Products, Inc	Vitamin C
Tri-Retinol Complex	SkinMedica	Retinol
Vitamin C+E Complex	SkinMedica	Vitamin C
White Lightening Complex	iS Clinical	Arbutin, licorice
White Lightening Serum	iS Clinical	Arbutin

Abbreviations: TA, tetrahexyldecyl ascorbate; HR, hexylresorcinol; 4-EB, 4-ethoxybenzaldehyde; LHA, lipohydroxy acid; GA, glycolic acid; DG, disodium glycerophosphate; PR, phenylethyl resorcinol; UP, undecylenoyl phenylalanine.

lentigines was maintained without the use of maintenance therapy, whereas HQ-induced skin lightening was not sustained.[43,45,46]

Kojic Acid

An effective skin-lightening agent found in OTC and office-based products, kojic acid (5-hydroxy-2-[hydroxymethyl]-4-pyranone) is a hydrophilic molecule derived from species of *Aspergillus* and *Penicillium,* acting as a tyrosinase inhibitor that chelates copper at the enzyme's active site. Kojic acid is the most popular agent used in Asia for the treatment of melasma,[4] and it is a common ingredient in cosmetic formulations in the United States, available OTC in a 2% concentration.[5] A known sensitizer, kojic acid is somewhat controversial despite its effective bleaching effect because of its mutagenicity and the ability to cause contact dermatitis, leading to its ban and later reinstatement as a pigment-lightening agent.[5,47-52]

In one split-face trial evaluating a glycolic acid and kojic acid combination versus a glycolic acid and HQ combination, investigators found no statistically significant difference between the 2 formulations for clinical efficacy, but the kojic acid–containing preparation was more irritating to patients.[47] A split-face trial by Lim[48] that evaluated a combination gel containing kojic acid, glycolic acid, and HQ showed more improvement (60% [24/40]) than a gel that contained only glycolic acid and HQ (47.5% [19/40]).

Following deoxyarbutin and kojic acid, the available pigment-lightening agents decrease in efficacy.[4,52] As a result, several manufacturers combine multiple agents in one formulation to inhibit pigment production through interruption of melanogenesis at various steps along the pathway.

Licorice Extract

Licorice extracts are skin-lightening agents with the fewest side effects.[4] In a split-face controlled study of 20 women with epidermal melasma who were treated with liquiritin cream, 80% (16/20) showed an excellent response, 10% (2/20) showed a good response, and 10% (2/20) showed a fair response.[53] One patient showed moderate improvement with the vehicle. Two patients developed mild irritation (erythema and burning sensation) with the liquiritin cream that resolved with continuation of the cream.[53]

Because of its benign profile, licorice extract is one of the most widely used agents in cosmeceuticals for skin brightening. It inhibits tyrosinase, leading to inhibition of melanogenesis.[54,55] The active ingredients are liquiritin, which disperses melanin, and isoliquiritin, glabridin, and licochalcone A. Licorice extract also has topical anti-inflammatory[4] and anticarcinogenic[5] properties. The anti-inflammatory properties help reduce erythema and PIH.[4] This ingredient can be integrated into facial foundations or moisturizers. It generally is applied topically in a dose of 1 g daily for 1 to 4 months to observe clinical result. However, the ingredient is quite expensive, and the concentration used in most preparations is modest.[53] Of note, licorice extract often is combined with ascorbic acid.[53-55]

Ascorbic Acid

Ascorbic acid, the reduced form of vitamin C, is an antioxidant that works by interrupting melanogenesis via interactions with copper ions to decrease dopaquinone and block dihydro-chinindol-2-carboxyl acid oxidation.[56] Because of ascorbic acid's limited stability and rapid oxidation, producing biologically active formulations is difficult. However, some ascorbate esters (magnesium-L-ascorbyl-2-phosphate) avert such outcomes.[5] The skin-lightening effect of ascorbic acid is poor when used alone; therefore, it is typically combined with licorice extracts and soy to increase efficacy, producing a minimally effective pigment-lightening formulation with an excellent safety profile. Ascorbic acid also is used in combination with HQ in extemporaneous compounded formulations. Such combination products are well tolerated in darker racial ethnic groups.[4,5,57]

In a split-face trial, Choi et al[58] showed that Korean women with melasma reported a noticeable improvement on the vitamin C–treated side, yet no long-term follow-up was implemented to establish the length of these effects. In another randomized split-face trial of 16 patients, HQ cream 4% yielded subjectively greater improvement than ascorbic acid cream 5% (93% vs 62.5%, respectively; $P=.001$). Ascorbic acid caused significantly less irritation than HQ; therefore, it may be a useful adjunct treatment in patients unable to tolerate HQ because of side effects ($P<.001$).[56]

Soy

It has been documented that the most commonly used skin-lightening agent in cosmetic moisturizers is a soy extract known as soybean trypsin inhibitor,[59] which inhibits the protease-activated receptor 2 pathway that is necessary to regulate keratinocyte phagocytosis of melanosomes and melanosome transfer.[59-61] Blockage of this pathway can reversibly inhibit melanosome transfer following 3 weeks of raw soy milk application. The adverse effects are minimal, leading to a favorable safety profile. Because only melanosome transfer is inhibited and not melanin production, the skin-lightening effect of soy is not as remarkable as HQ.[4,61,62] Following 12 weeks

of application, the soy formulation proved efficacious in lightening mottled pigmentation and solar lentigines.[63] An 8-week trial of Southeast Asian patients with solar lentigines revealed decreased melanin density ($P<.05$) and melanin area ($P<.01$).[64] Another study showed that inhibition of this pathway produced a dose-dependent loss of pigmentation as early as 4 weeks at the highest tested dose.[65]

Aleosin

Acquired from the aloe vera plant, aleosin is a natural hydroxymethylchromone that competitively inhibits tyrosinase at the dihydroxyphenylalanine oxidation site.[66,67] In a study using pigmented skin equivalents (human keratinocytes and fibroblasts), aleosin induced dose-dependent reduction in tyrosinase activity and melanin content without changing the morphology of the cells, suggesting a good safety profile.[68] Compared to HQ, aleosin exhibits no cell cytotoxicity; however, its hydrophilic structure limits its ability to penetrate the skin. It is commonly used in formulation with arbutin or deoxyarbutin to reduce tyrosinase activity through various mechanisms.

Niacinamide

The water-soluble derivative and physiologically active form of niacin is niacinamide, which has been used in the treatment of acne. Niacinamide's mechanism of action is different from HQ, as research shows that niacinamide does not inhibit tyrosinase or melanogenesis; it also does not alter the viability or number of melanocytes.[10] Niacinamide is a component of some OTC lightening agents. Hakozaki et al[69] demonstrated its ability to improve photodamage in 18 Asian subjects with hyperpigmentation, showing that the use of niacinamide moisturizer 5% produced a significant reduction in facial hyperpigmentation ($P<.05$). In a 10-week, double-blind, vehicle-controlled study conducted in women aged 40 to 60 years, the combination of 4% niacinamide plus 2% *N*-acetylglucosamine reduced the appearance of hyperpigmentation to a greater degree than SPF 15 sunscreen alone.[70]

N-Acetylglucosamine

Another cosmetic skin-lightening agent, *N*-acetylglucosamine is an amino monosaccharide produced by the body through the addition of an amino group to glucose.[71] In addition to tyrosinase inhibition, *N*-acetylglucosamine has several roles within the body, including functioning as a substrate for the production of hyaluronic acid, heparan sulfate, and proteoglycans, which are important substances in maintaining the water content of the dermis. In a randomized double-blind clinical study that used topical 2% *N*-acetylglucosamine twice daily for 8 weeks, the agent produced modest pigment lightening.[72]

CONCLUSION

Hyperpigmentation is a common dermatologic condition affecting all skin types, particularly Fitzpatrick skin types IV to VI. Pigment lightening is an integral component of dermatologic therapy, and there are many safe treatments with varying degrees of efficacy that can be employed. Adding sunscreen to the treatment regimen and patient education regarding sun protection measures also will be beneficial in the management of patients with PIH. The management of hyperpigmentation can be challenging, not only because of the nature of the condition but also because patients may self-medicate using a myriad of OTC agents made in the United States and abroad that are unregulated. Dermatologists can effectively manage potential adverse outcomes by having candid discussions with patients regarding all topicals being used and asking patients to bring in these agents during office visits.

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