The Role of Cosmeceutical Compounds in Dermatologic Disease States

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Upon completion of this article, the pharmacist should be able to:
1. Explain the rationale and advantages of compounding to treat topical dermatologic disease.
2. Discuss the pathophysiology of the dermatologic disease states of acne and atopic dermatitis.
3. Describe the role of current therapy in treating dermatologic disease states of acne and atopic dermatitis.
4. Identify the appropriate active ingredient for use in a cosmeceutical product to treat a specified dermatologic disease state based off of its intended mechanism of action.
5. Identify opportunities for compounding dermatologic treatments in community pharmacy.

Pharmaceutical compounding is deeply rooted in the origins and history of pharmacy. Historically, pharmacist-compounded prescriptions were the most commonly dispensed entities. During the 1930s, approximately 75 percent of all prescriptions required some form of compounding. However, recent numbers estimate that figure has decreased to approximately 1 percent to 8 percent of all prescriptions. Conversely, compounding is experiencing a resurgence as there is an increased demand for individualized patient medications from various health care professionals. According to the Food and Drug Administration (FDA), traditional pharmacy compounding involves the “extemporaneous combining, mixing, or altering of ingredients by a pharmacist in response to a physician’s prescription to create a medication tailored to the specialized medical needs of an individual patient.” The key phrase to recognize in the FDA’s statement is that compounding is performed by a pharmacist. Performing such a task should be done by a health care provider who possesses the knowledge and proper skills needed for compounding: the pharmacist. Although the FDA, physicians, and patients recognize the importance of compounding, regulatory changes have threatened to affect the way in which pharmacists practice compounding. As a result, several professional compounding organizations exist to protect the right of pharmacists to continue compounding practices.

While patients of every age can benefit from compounded pharmaceutical products, there are certain patient populations that may represent a special niche in this area. One example would be the pediatric and geriatric populations. These patients often require specialized dosing or dosage forms due to age-related issues that only compounding can provide. Other patients who may benefit from compounded preparations include patients unable to swallow a tablet or capsule, patients unable to tolerate large dosage forms or multiple oral medications, patients with allergies to excipients found in commercial medications, or those with unique medical conditions. In these instances, compounding can be used to improve...
overall patient safety and compliance with their medication regimen. Compounded products can be prepared to meet individual patient-specific needs. Examples of specialized compounding could include making preparations that are preservative-free, fragrance-free, dye-free, prepared with natural ingredients, or with penetration enhancers to aid in delivery through the skin. Some conditions with dermatologic manifestations that may require specialized compounds include acne, psoriasis, eczema, sunburn, scarring, warts, rosacea, baldness, and wound care, among many others. With the combined training and versatile knowledge of available products, pharmacists can prepare truly unique preparations to meet their patients’ needs. This sort of practice helps brand the pharmacist and their business in the eyes of the customer, providing the opportunity to increase overall profitability of their pharmacy.

Compounding is often associated with a physician-ordered prescription; however, it can also involve over-the-counter (OTC) products. Many pharmacies have found it rewarding to compound their own line of OTC products to better serve their clientele. By understanding the needs of their particular patients, pharmacists have the ability to prepare and sell customized compounded OTC products. Another popular avenue is cosmeceutical compounding; a relatively new area of compounding that provides the therapeutic effects of cosmetics as a function of their formulation.

While the opportunity for cosmeceutical preparations is vast, four specific categories stand out as significant opportunities for cosmeceutical compounds: acne, atopic dermatitis, anti-aging products, and skin lightening agents.

**ACNE VULGARIS**

Acne vulgaris is the most common skin condition in the United States. Commonly referred to simply as acne, it affects approximately 40–50 million Americans, with the majority being teenagers. Despite the high prevalence of acne, patients may be reluctant to seek treatment from a health care professional and prefer OTC agents to clear the lesions as a first option. Due to the complex pathophysiology of acne, a health care provider’s recommendations are crucial to effectively treat this disease. Furthermore, early and proper treatment of acne minimizes the risk of permanent scarring. There have been several studies that investigated the link between acute acne outbreaks and psychological disorders, including depression, anxiety, social isolation, assertiveness, anxiety, and body dissatisfaction. There appears to be an exponential worsening of these psychological symptoms in acne sufferers with increasing age. There is a social stigma associated with adult acne that may result in embarrassment, social withdrawal, and a higher unemployment rate. In an adult acne study to determine the most bothersome aspect of the disease state, both men and women equally responded with “appearance.” Acne is a very treatable skin condition and the community pharmacist is well positioned to recommend appropriate OTC treatment or refer patients to a physician if required.

To understand acne’s progression from mild to severe, it is important to be familiar with the pilosebaceous unit (PSU), also referred to as the pilosebaceous duct or sebaceous gland. The PSU is composed of a hair follicle, hair muscle (arrector pili), and sebaceous glands. Before puberty, the hair within the PSU is vellus (fine) and non-pigmented, commonly referred to as “peach fuzz.” The growth of this vellus hair is not affected by hormones. However, during puberty, testosterone is converted to dihydrotestosterone (DHT), which stimulates the PSU to become either a terminal hair follicle or sebaceous follicle. Terminal hair follicles are the large, heavily pigmented hairs such as facial, groin or axillae hair. The PSU is a ubiquitous microscopic gland found throughout the body except for the palms, soles, dorsa of feet, and lower lip. Conversely, sebaceous glands are found on the face, chest, back, and upper/outer arms, some of the most common sites for acne breakouts. While DHT acts on sebaceous glands to increase their size and metabolic rate, estrogen works as an antagonist to decrease sebaceous gland secretion, which is an important point when determining appropriate treatment options. Testosterone is not the only hormone involved in the initial stages of acne; evidence suggests a correlation between the development of acne and increased androgen levels. Toward the end of puberty, when androgen levels stabilize, acne tends to wane. Despite hormone involvement, current guidelines recommend against routine endocri-
nologic testing in the majority of acne patients. Signs of elevated androgen levels include body odor and axillary or pubic hair in young patients; in adult women, symptoms such as recalcitrant (late-onset acne), infrequent menses, or hirsutism are possible. Adult male and female pattern alopecia, infertility, and truncal obesity (in addition to acne) indicate hormonal imbalances that require physician evaluation.

The first step in the progression of acne vulgaris is increased sebum production in the PSU, often occurring simultaneously with hypercornification of the PSU. Under normal circumstances, sebum functions to decrease water loss from the skin surface and to protect the skin from infection. During times of increased hormone production, sebaceous gland secretion is increased within the PSU. Sebum itself is the pathogenic source in acne, with most patients presenting with higher than normal sebum levels. Although sebum is irritating and comedogenic, combining sebum with the process of hypercornification leads to the first lesion of acne, the microcomedo. Hypercornification, also known as hyperkeratinization, occurs when there is an increased number of cells attached to the follicular canal (directly above the opening of the sebaceous gland duct) to form a plug known as the microcomedo. The exact pathogenesis of hyperkeratinization is not entirely understood. However, lipid composition, androgens, and local cytokines are all thought to play a role. The microcomedo is a non-inflammatory form of acne and results in either an open or closed comedone, which is a plug of sebaceous and dead skin material stuck in the opening of the PSU. Common terms for these lesions are blackheads (open comedone) or whiteheads (closed comedone). A whitehead, or closed comedone, is formed when the pore becomes clogged (due to the previously stated desquamation process) and there is increased sebum production in the sebaceous glands. The result is the formation of a firm, white papule, or “whitehead.” If the follicular pore dilates, the contents inside are exposed to air, which often results in a black-like color, thus forming the open comedone, or “blackhead.” Figure 1 illustrates the primary acne lesions of the microcomedo, open comedone, and closed comedone.

Acne can eventually progress to an inflammatory disease beyond the initial open and closed comedone lesions. Inflammatory acne is characterized by the formation of papules and pustules, and can be categorized as mild, moderate or severe based on the number of lesions. Progression from non-inflammatory to inflammatory acne occurs when there is an increase in the microbial flora, specifically *Propionibacterium Acnes* (P.Acnes). P.Acnes, an anaerobic organism, live in the pilosebaceous follicle under normal conditions. However, increased sebum production causes this organism to proliferate and contribute to the inflammatory response. The severity of inflammation is patient-specific and depends on the individual’s hypersensitivity to the acne-forming process.

Based on the complex pathophysiology of this condition, it is important to recommend treatment that targets the appropriate causative factor of the patient’s acne. A treatment that is comedolytic inhibits the formation of comedones and will not reduce the population of P.Acnes. Similarly, a treatment aimed at reducing sebum may not be effective in reducing inflammation. There is a significant and expanding OTC market for acne treatments. As the majority of patients will not seek physician treatment for acne, OTC products are an extremely popular self-treatment avenue for patients with mild to moderate disease. There are a variety of active ingredients found in OTC acne products, such
as benzoyl peroxide, salicylic acid, sulfur, sodium sulfacetamide, alpha hydroxyl acids, and tea tree oil, to name a few. Again, to recommend the appropriate OTC treatment, it is crucial to understand which underlying causative factor of acne the active ingredient is targeting.

Two of the most common ingredients in OTC acne products are benzoyl peroxide and salicylic acid. Benzoyl peroxide (BPO) is primarily antibacterial, and also has antikeratolytic and comedolytic properties. Due to BPO’s varying actions, inflammatory acne lesions and comedonal acne are typically diminished with this medication. BPO can be used as monotherapy or in combination with prescription antibiotics or retinoids. One major advantage to using BPO is the lack of bacterial resistance to this product. Unlike topical retinoids, BPO is unaffected by sunlight, allowing for application in either the morning or evening. Common adverse effects of BPO include dry skin, which can lead to scaliness, peeling, and (in severe forms) cracking. Counseling patients to apply a thin layer of the medication is recommended. Patients should adapt to the side effects of this medication within a week or two. It is important to educate patients that benzoyl peroxide can cause bleaching of clothing and hair. Salicylic acid, the other commonly used OTC acne treatment, has both keratolytic and comedolytic properties. It may be used as initial therapy for mild acne or as an adjunctive agent in broader therapeutic regimens. A placebo-controlled study of 114 patients revealed that 2 percent salicylic acid lotion demonstrated a statistically significant improvement over baseline in patients at 12 weeks. Adverse effects to topical salicylic acid are minimal but could include skin irritation, redness of the skin, or dryness and peeling.

Several other OTC acne treatment ingredients are available to help treat mild acne, but these are used less frequently than BPO or salicylic acid. Sulfur, now rarely used, has keratolytic properties resulting from the formation of hydrogen sulfide through the reaction of the sulfur with keratinocyte cells. Sulfur has a distinguishable unpleasant odor, is often seen in combination with salicylic acid or resorcinol, and may cause dry skin. Sodium sulfacetamide, an antibacterial agent, can be seen in combination with sulfur in prescription products (sodium sulfacetamide 10 percent, sulfur 5 percent). Sodium sulfacetamide is also available in formulations without sulfur in preparations such as a topical foam and gel. Alpha hydroxy acids (AHA’s), such as glycolic acid and lactic acid, are preferred by some patients since they are viewed as “natural” substances. AHA’s work by reducing the thickness of the stratum corneum, the uppermost layer of the skin. Due to their mechanism of action, there is a multitude of uses for AHA’s in addition to acne, including use as exfoliants, treatment of seborrheic dermatitis, scarring, dry skin and hyperpigmentation. Lastly, tea tree oil has anecdotal success in treating various skin conditions. In a single-blind trial of 124 patients, 5 percent tea tree oil gel was compared to 5 percent benzoyl peroxide lotion in the treatment of mild-to-moderate acne. Both agents significantly reduced the number of comedones and inflammatory lesions. However, the benzoyl peroxide was superior in reducing the number of lesions and having a faster onset of action.

Although OTC products can be useful in treating mild forms of acne, there are a vast number of prescription treatments available to target the possible different causes of acne. Topical retinoids are considered first-line agents and are used in treating mild, moderate and even some severe cases of acne. Retinoids may be used alone or in combination with an antimicrobial agent, depending upon the degree of inflammation. Topical tretinoin (all-trans-retinoic acid) is a highly effective comedolytic agent that normalizes keratinocyte desquamation by influencing follicular epithelial turnover. Topical tretinoin is available in both gel and cream formulations, and selection of dosage form depends on the sensitivity of the patient’s skin and current climate. For example, alcohol-based gels are more irritating than cream-based products. Gels are preferred in hot and humid climates and creams in cold and dry climates. As topical tretinoin is notorious for causing skin irritation, counsel patients to begin with a small application of the product and gradually increase to minimize any exacerbation or irritation. Another important counseling point is that tretinoin is unstable in UV light as well as in combination with benzoyl peroxide. Therefore, it should be applied in the evening and separated by one to two hours from the application of BPO if the two are used concomitantly. Adapalene, another topical retinoid, is stable both in UV light
and in combination with BPO, and is generally well tolerated by patients. Tazarotene, a synthetic naphthoic acid derivative with retinoid activity, is an effective and photo stable topical retinoid. However, there have been several reported cases of dermatitis, making the use of tazarotene less popular. Systemic isotretinoin is highly efficacious in controlling acne and ensuring long-term remissions. Mechanistically, isotretinoin targets all four major causes of acne: increased sebum production, hypercornification of the pilosebaceous unit, increased P. Acnes, and inflammation. In addition, the effects of isotretinoin extend beyond discontinuation of therapy. One major limitation to isotretinoin use is the risk of serious adverse events. Commonly reported adverse effects of isotretinoin include arthralgias, elevated serum lipid concentrations, depression, psychosis, suicidal ideation (black box warning), and teratogenicity. Safety programs for isotretinoin use include a risk evaluation and mitigation strategy (REMS) program, and the iPledge program, which is designed to ensure patient education on the medication prior to use.

Antibiotics were once considered the standard of treatment for acne. However, increasing antimicrobial resistance rates suggest antibiotics should not be used as monotherapy. Topical antibiotics, such as erythromycin, clindamycin and metronidazole, are useful for mild pustular or comedogenic acne. Antibiotics work to eradicate P. Acnes, along with decreasing the inflammatory response to acne. Topical antibiotics are often used in combination with benzoyl peroxide. Oral antibiotics are typically reserved for treatment of moderate-to-severe acne. Common oral antibiotics used for acne treatment include tetracycline, doxycycline and minocycline. Erythromycin or clindamycin are recommended for use in children or pregnant women, due to the adverse event profile of tetracyclines in these populations. However, it is important to recognize that P. Acnes exhibits greater resistance to erythromycin than tetracycline. Treatment with oral antibiotics should continue for six to eight weeks for minimum improvement, and the antibiotic should be discontinued once improvement is noted. Topical retinoids, however, should be continued to maintain the improvement in acne control.

Systemic medications that alter sebum production include estrogens and spironolactone. Estrogens, usually prescribed as a combined estrogen-progestin contraceptives, show beneficial effects at doses of ≥50μg of ethinyl estradiol (or equivalent). New oral contraceptives that contain ≤35μg of ethinyl estradiol are less effective in suppressing sebum production. However, they have still shown effectiveness in treating acne while reducing unwanted side effects such as weight gain, and they are FDA-approved for this indication. Other studies have compared the effects of different forms of progestins, in combination with ethinyl estradiol, on acne outcomes. One particular study found that although the progestins levonorgestrel and norethindrone acetate altered secondary markers differently, they both improved acne and were well-tolerated. A minimum of two to four months is required before a significant improvement in acne control is noted with these agents. Contraindications to using oral contraceptives include smoking, migraine headaches with aura, and hypertension. Spironolactone reduces sebum production in doses of 100–200 mg/day, but may be effective with even lower doses. Four studies looked at the use of spironolactone either alone or as an adjunct in doses of 50–200 mg/day and showed a 50–70 percent improvement of acne. As with estrogens, a few months of spironolactone therapy may be required for an improvement in lesions.

Although plenty of OTC and prescription acne treatments are available, compounding for acne patients is still a routine practice. Cosmeceuticals can be very profitable as it empowers the pharmacist to utilize several different compatible ingredients to optimize the patient’s acne regimen. One example is catering to a patient with sensitive skin who requires an acne treatment with an increased moisturization effect. The previously listed medications can be formulated into a custom compound with a thick, moisturizing cream base. As mentioned earlier, the AHA’s can be useful in treating acne due to their actions as keratolytics and exfoliants, which results in skin turnover. Specific AHA’s that can be used in compounding in this fashion include glycolic acid, mandelic acid, and lactic acid. One major caution when compounding with AHA’s is the decreased stability of
the preservative in the overall compound. Hydrophilic ointments produce the most stable creams in combination with AHA’s. However, they will decrease preservative levels and reduce the compound’s overall shelf life.

**ATOPIC DERMATITIS**

Atopic dermatitis, often referred to as eczema, is another disease state in which pharmacists can play an important role by counseling patients on treatment options and preventative measures. Eczema is a chronic skin disorder that involves scaly and itchy rashes, along with blistering, weeping or peeling skin. The most common type of eczema is atopic dermatitis (AD). Atopic dermatitis primarily affects children and follows a remitting/flaring course that may continue into adulthood. Approximately 10–20 percent of children develop atopic dermatitis, whereas only 1–3 percent of adults are affected. For the majority of children (~60 percent), atopic dermatitis develops within the first year of life, and 80 percent of patients experience the first symptoms before the age of 5. Atopic dermatitis appears to have an increased prevalence in industrialized countries. However, there is equal prevalence in both genders, and disproportionate prevalence with regards to race. The largest difference between atopic dermatitis in children and adults is in the areas of presentation on the body. The most predominant and classic symptom of AD, regardless of the age of the patient, is pruritis. Excoriation (scratching) of this pruritis exacerbates the hyperirritable skin and results in inflammation. An important educational point to remember is that the pruritis precedes the visible eruption and inevitable inflammation of the skin, not the other way around. In other words, “it is not the eruption that is itchy, but the itchiness that is eruptive.”

The pathophysiology of atopic dermatitis is not completely understood, and a multitude of factors have been proposed to play a role. The majority of patients with AD have a family history of allergic rhinitis or asthma (called the “atopic triad” when all three disease states occur concomitantly), and thus are often told that their disease is due to allergies. Individuals with AD tend to have respiratory allergies, but the skin manifestation is not due to an allergic reaction. If these patients undergo a skin test for allergies, the skin will commonly react and the patients are then informed they are allergic to “everything,” which is inaccurate. In reality, the skin is reacting to the invasion of the needle due to its hyperirritable state, which is not a true manifestation of allergies. Patch skin testing may prove beneficial if the patient presents with difficult-to-treat AD or other allergic symptoms. Avoiding allergens is often considered a first-line approach to managing AD, despite minimal noted improvement of dermatitis. The skin of patients with atopic dermatitis presents an increased number of T-helper type 2 cells; whereas chronic AD lesions exhibit greater eosinophil infiltration. Eosinophil counts are roughly correlated with disease severity. The role of Immunoglobulin E (IgE) in atopic dermatitis is currently unknown.

Diagnosis of AD is primarily based on observation of the skin in addition to patient and family history. Major features of atopic skin required for diagnosis include pruritis, chronic or chronically-relapsing dermatitis, and typical morphology and distribution of the disease based on age. In children, AD commonly presents on the cheeks and extensor surfaces of the arms and legs. In adults, flexural surfaces and hand dermatitis are more common. Other universal findings in patients with AD include heilitis (inflammation of the lip), recurrent conjunctivitis, xerosis (dry skin), and cutaneous infections (secondary to excoriation to the skin).

Current treatment of AD is aimed at eliminating inflammation and pruritis, with first line being irritant and allergen avoidance. Treatment also includes restoring the stratum corneum barrier, and controlling exacerbating factors. The stratum corneum, or outermost layer of the skin, serves as the permeability barrier of the skin. It prevents the loss of necessary fluid and electrolytes, regulates body temperature, and prevents entrance of harmful microbes and UV light. Recommending the appropriate moisturizer is essential in restoring the stratum corneum barrier. Common ingredients found in moisturizers include water and occlusive and humectant agents. Water alone produces only a transient increase in hydration of the skin. When water is placed on the skin, a small
amount will penetrate and dampen skin; however, it is subject to evaporation. Therefore, the best moisturizers include both a humectant and occlusive agent in addition to water. Humectants attract and trap water from the dermis (layer of skin below the hyperdermis) as well as the outside environment. Examples of agents with humectant properties include glycerin, sodium lactate, propylene glycol, urea, hyaluronic acid, and panthenol. Occlusive agents provide a hydrophobic film on the skin to prevent water loss. Occlusive agents are often described as “greasy” and include petrolatum, mineral oil, lanolin, paraffin, or silicone derivatives (dimethicone and cyclomethicone).

Aside from irritant avoidance, other treatment options for patients with AD include topical corticosteroids, antibiotics for secondary cutaneous infections, antihistamines (sedating antihistamines preferred), phototherapy or immunomodulation with either tacrolimus or pimecrolimus (for severe cases). Immunosuppressive therapy should not be used in children less than two years of age.

There are several nonpharmacologic counseling tips to help patients or parents of patients with AD manage the disease. For starters, instruct patients to take lukewarm baths (as extremely hot temperatures may cause vasodilation, worsening pruritis), lasting only 10–20 minutes. Unscented soaps with a neutral pH are preferred as these are the least irritating. After bathing, the patient should be instructed to immediately apply a moisturizer to the damp skin. Since atopic skin tends to be extremely dry, an ointment-based moisturizer is recommended. Patients could also use everyday items such as vegetable oil to moisturize the skin if they are seeking a more cost-effective alternative. For children experiencing repeated cutaneous infections due to scratching of the skin, parents can add household bleach to the bathwater (two teaspoons per gallon of water). Other lifestyle modifications include avoidance of rough, wool clothing, using liquid rather than powder detergents, avoiding smoking in the home, using a humidifier, and avoiding topical products containing alcohol or astringents.

While the majority of treatments for AD are aimed at trigger avoidance and moisturization of the skin, compounding opportunities exist in compounding specific types of moisturizers for these patients. Due to their hyperirritable skin, a need exists for cosmeceutical moisturizing agents prepared without irritating excipients. Tailoring the type of moisturizer to a child suffering from AD will not only ease their symptoms, but also ease the minds of their caregivers.

ANTI-AGING

Anti-aging products represent one of the most popular avenues of cosmeceutical products. Despite the inevitable process of aging, which affects every organ of the human body, and most notably, the skin, societal pressure leads patients to attempt to fight this phenomenon. As the life expectancy and population continue to increase, more consumer money is spent in the field of anti-aging. It is estimated that one-fifth of Americans will be 65 or older by 2030. Furthermore, life expectancy in major industrialized nations will continue to rise, potentially reaching 100 years by that same year. In 2008, it was estimated that approximately $333 billion dollars were spent on cosmetics, with cosmeceuticals representing $2.5 billion of that amount. Even in the current recession, cosmetics, and in particular, anti-aging products, continue to stay positive in terms of growth. It appears that people, more than ever, are seeking non-surgical alternatives to combat signs of aging. Other studies have estimated that nearly 90 million Americans have used an anti-aging product at some point in their lifetime. This statistic is not surprising as the baby boomer population continues to age. Patients are concerned with health, fitness and appearance now more than ever, and compounding of anti-aging products is a lucrative field.

As always, it is important to understand the underlying causes of aging skin in order to recommend appropriate treatments or to compound cosmeceuticals using the suitable active ingredients. There are several causative agents in the various features of aged skin, both intrinsic and extrinsic. Intrinsically, proposed mechanisms of aging deal with oxidative stress, genetics, and metabolism. Extrinsically, culprits such as pollution and smoking play a role,
but one of the biggest perpetrators of aging is ultraviolet (UV) light damage. Photo aging, which is the influence of solar UV radiation on the skin, accounts for approximately 80–90 percent of visible skin damage related to aging. UV light causes a breakdown in elastin, which, along with collagen, is one of the major skin proteins responsible for skin’s elasticity, tone, and texture. With a breakdown in elastin, skin loses its flexibility and ability to “snap back” into place. Melanocytes, cells that produce the UV protective pigment melanin, also tend to decrease with age. With less melanin, older patients are more susceptible to UV light’s effect. Impairment of collagen and elastin structure is typically more pronounced in photo aged skin compared to naturally chronically aged skin. Skin cell turnover also tends to slow down as we age, leaving excess dead skin cells on the surface. Another phenomenon frequently observed in aging skin is a generalized thinning of the skin. This is caused by a loss in the underlying fat layer of the skin. Bone loss is also exacerbated with age, resulting in a noticeable puckering of the skin around the nose, mouth, and chin. Lastly, the skin is considered a good indicator of overall health inside the body. Years of poor eating habits, stressful lives, and poor lifestyle choices are manifested in the outside appearance.

There are many surgical treatments available to reverse the signs of aging. Microdermabrasions, chemical peels, lasers, face lifts, and botulinum toxin injections are popular means to restore a more youthful appearance. However, these procedures can be expensive, inconvenient, and have serious adverse reactions. Prescription topical retinoids, such as tretinoin or tazarotene, also have a role in anti-aging medicine. However, these products cause local side effects such as burning and stinging. For these reasons, OTC anti-aging products are appealing, convenient, and cost effective to the general public. The next section discusses some of the available treatments to prevent and treat photo aged skin, along with ingredients available for compounding anti-aging products.

One basic way to treat photo aged skin is to prevent the damage from occurring. This includes measures to protect the skin from UV radiation, such as applying sunscreens, wearing sun-protective clothing, and limiting sun exposure, particularly during peak sun times. Sunscreens are broadly defined as agents that protect against UV damage and prevent or minimize sunburns, wrinkles, and pigmentary changes. Protecting the skin from UV damage results in minimal signs of aging. Sunscreens in the United States are regulated as OTC drugs by the FDA. As sunscreens are classified as a drug, this affects advertising of cosmeceutical products containing SPF (sun protection factor) properties. The FDA has specific labeling requirements for sunscreens, including SPF and water resistance, which is gauged by their maintenance of SPF after being emerged in water for either 40 or 80 minutes (“water-resistant” versus “very water-proof”).

An older class of ingredients used in anti-aging formulations is the alpha hydroxy acids (AHA’s), previously discussed in the acne section. The anti-aging properties of the AHA’s have been recognized for centuries, and are still popular components in both commercial and compounded products. AHA’s can be used in a variety of concentrations, depending on the desired effect. When applied topically in low concentrations, AHA’s have both an exfoliation and moisturization property. The exfoliant property is a result of decreased epidermal cell cohesion, which leads to increased shedding of the skin. Exfoliation provides immediate smoothing of the skin, resulting in a more uniform appearance. When used in a higher concentration, AHA’s can cause separating of the upper epidermis from the dermis, known as a chemical peel. AHA’s also have a moisturizing effect to the skin by aiding in the retention of water within the epidermis. This assists in diminishing the appearance of fine wrinkles. When compounding with AHA’s, it is important to choose the proper vehicle. For patients with extremely dry skin, creams are preferred; whereas lotions are less occlusive for combination-type skin (mixture of dry and oily skin). If the patient is prone to acne or has oily skin, an alcohol-based product should be used due to its drying effect on the skin.

Other popular anti-aging cosmeceuticals incorporate antioxidants. The skin is continuously exposed to oxidative stress leading to accelerated aging by damaging DNA, lipids, and proteins. Antioxidants are believed to
protect the skin from photo damage through decreasing the ability of UV radiation to produce free radicals. They also work by inhibiting inflammation which can lead to collagen depletion. Examples of substances with antioxidant and anti-aging properties include vitamins E and C, coenzyme Q10 (CoQ10), idebenone, and ferulic acid. Vitamin C, or L-ascorbic acid, has clinical data that supports its use to reduce fine lines as well as reducing inflammation and hyperpigmentation. Despite this evidence, most cosmeceutical formulations containing vitamin C are ineffective, likely due to the fact that exposure of vitamin C to air and light compromises its stability. Vitamin E (α-tocopherol) has limited clinical efficacy when used topically. It has been shown to have a synergistic effect when used concomitantly with vitamin C. Ferulic acid, when used in combination with vitamins A and E, has greater antioxidant properties than either of the vitamins alone. CoQ10 works as an antioxidant to scavenge for free radicals. Although evidence exists for its use in-vitro, clinical data is still lacking. The use of idebenone has been studied in various disease states including cardiomyopathy and Alzheimer’s Disease, but its use as an anti-aging agent is due to its mechanism of action as a free radical scavenger and electron carrier. Research has shown that, in terms of antioxidant properties, idebenone is superior to vitamin E, CoQ10, and vitamin C.

Other sources of active ingredients in anti-aging cosmeceuticals could include green tea extract, grape seed extract, Morinda citrifolia, and peptides. Both green tea and grape seed extracts are considered botanical ingredients, meaning their use is unregulated and most likely unsupported by clinical data. Green tea polyphenols has been shown by studies to possess chemoprotective properties and are useful against inflammatory responses of skin exposed to solar radiation. A challenge remains with compounding products with green tea polyphenols as they are highly unstable and will oxidize easily. Grape seed extract possesses antioxidant properties much like green tea, and has also been shown to speed wound contraction and closure. Morinda citrifolia is a fruit extract and upregulates the biosynthesis of collagen and glycosaminoglycans. Finally, the theory of using topical peptides in cosmeceutical products is increasing in popularity. A peptide is a short chain of amino acid sequences that makes up a larger protein. The theory behind peptide use in anti-aging products is that the small chain peptides may be able to imitate biological processes to stimulate repair while inhibiting processes that accelerate aging. Peptides that are currently being studied for anti-aging properties include TGF-β and KTTKS.

HYPERPIGMENTATION

Hyperpigmentation is a common, usually benign, condition in which patches of skin present with a darker color than the surrounding area. This phenomenon can occur in any gender or race and is a result of excess melanin. Recurrent solar damage to exposed areas, such as the hands and face, may result in what is called solar lentigines. These are common in the elderly population and are often referred to as “age” or “liver” spots (despite having no connection with the liver organ). Solar lentigines (singular: lentigo) are most common after the age of 40 and are light brown- to- black macules varying in size from 0.2 to 2cm. These lentigines commonly occur on the forearms or shoulders, as well as on the face and hands. People with light-colored or fair skin, or those with a history of frequent or intense sun exposure or burn, are most at risk for developing solar lentigines. Solar lentigines are usually benign, but a biopsy should be performed if they present with an irregular border, localized increase in pigmentation, or localized thickening. Although they are commonly interchanged, lentigines are different from freckles. Freckles, or ephelides, tend to decrease in number with age, and become equally distributed on the face, arms and trunk. Although sunlight does promote freckles (they tend to fade in the winter), they are distinctly different from lentigines. Lentigines, caused by solar radiation, become more prevalent with age. They are also more common in males, whereas freckles are more common in females.

Other examples of hyperpigmentation of the skin include melasma, café-au-lait spots, diabetic dermopathy, and postinflammatory hyperpigmentation. Melasma, or the “mask of pregnancy,” is a symmetric brown hyper-
pigmentation on the face and neck of genetically predisposed women. Despite its nickname, melasma does not necessarily occur during pregnancy. It can affect anyone, although young women with brownish skin tones are at greatest risk. Melasma is associated with estrogen and progesterone, and therefore is more common in pregnant women, those taking birth control pills, or those taking hormone replacement therapy. Other lesser causes of melasma include thyroid dysfunction, phototoxic or antiseizure medications, and certain cosmetics. Melasma may or may not fade after pregnancy or cessation of the causative medication. Even after fading, melasma can return with subsequent pregnancies or initiation of causative medications. Café-au-lait spots, which are pale brown macules, can be found on any cutaneous surface. They may be present at birth and increase in number and size with age. Depending on the child’s age, greater than five or six of these spots may be indicative of neurofibromatosis. Another type of hyperpigmentation, diabetic dermopathy, is the most common cutaneous marker of diabetes mellitus and is present in 40 percent of patients with diabetes. These lesions are asymptomatic, round, hyperpigmented areas of skin that are usually indicative of internal complications. Lastly, postinflammatory hyperpigmentation occurs following chronic inflammation, often in poorly vascularized areas. The skin remains thickened and dark brown even during noninflammatory conditions.

The majority of the aforementioned types of hyperpigmentation are permanent fixtures of the skin, but may be treated with skin lightening creams or procedures. The most effective treatment for any cause of hyperpigmentation is prevention by exercising smart sun protection. Examples of this include wearing protective clothing in the sun, using high quality sunscreens, and avoiding the sun at midday, when it is most intense. Topical and surgical treatments of hyperpigmentation depend on the cause of the disorder. For lentigines, cryotherapy (using extreme cold to freeze and destroy tissue), is effective, but can result in hypopigmentation. Topical 0.1 percent tretinoin cream or 0.1 percent tazarotene cream have also shown promising results. Melasma is more difficult to treat. Types of treatment for melasma include hypopigmenting agents, chemical peels, and lasers treatments. Of the hypopigmenting agents, hydroquinone is the most effective. Certain countries have banned the use of hydroquinone due to permanent depigmentation and claims of carcinogenicity. Other reports have shown carcinogenicity only in animal studies using long-term exposure to hydroquinone at high doses. Hydroquinone is available OTC in strengths up to 2 percent and in prescription strengths of 3–4 percent. It may also be compounded in strengths as great as 10 percent. Hydroquinone should be applied twice daily (morning and evening), and patients should be cautioned that skin sensitivity is common. Other treatments for melasma include a cream containing a combination of 4 percent hydroquinone, .05 percent tretinoin, and .01 percent fluocinolone acetonide, applied once daily for eight weeks. Topical tretinoin and azelaic acid are also used in treating melasma. Café-au-lait spots may also be managed by hydroquinone bleaching treatments. If diabetic dermopaty or postinflammatory hyperpigmentation is suspected, referral for disease treatment should occur before aesthetic treatment of the area.

REGULATIONS FOR COSMECEUTICAL COMPOUNDING

Disclaimer: When it comes to compounding cosmeceuticals, a blend of cosmetics and active pharmaceutical ingredients, many legal questions come into play. Pharmacists often question what may or may not be compounded without a prescription, what types of logs need to be kept, or how to advertise these products. Although the regulations regarding cosmeceutical compounding are somewhat ambiguous, this section is meant to give a brief introduction into some of the regulations of cosmeceutical compounding. Any pharmacist interested in pursuing compounding of cosmeceuticals further is encouraged to investigate the legalities of compounding cosmeceuticals.

The first major distinction when dealing with cosmetic compounding is to differentiate between a cosmetic and a drug. The Food, Drug, and Cosmetic Act (FD&C Act) defines drugs as “articles intended for use in the diagnosis, cure, mitigation, treatment or prevention of
It further defines drugs as “articles [other than food] intended to affect the structure or function of the body of man or other animals.” A cosmetic, on the other hand, is defined as “an article intended to be rubbed, poured, sprinkled, sprayed on, introduced into, or otherwise applied to the human body or any part thereof for cleansing, beautifying, promoting attractiveness, or altering the appearance.” It is important to note that in these definitions, there is a clear distinction that drugs are meant to affect the structure or function of the body, whereas cosmetics only alter the appearance. This is an important key point in differentiating between a cosmetic and a drug, and thus, understanding which regulations to follow. Drugs are regulated by the FDA. Cosmetics are regulated under two laws: the Federal Food, Drug, and Cosmetic Act and the Federal Fair Packaging and Labeling Act (FPLA). Most of these regulations deal with labeling, though they also define cosmetics and drugs and address what entities or persons must register with the FDA.

Another important factor when differentiating between a drug and cosmetic is that the intended use of the product often determines its regulatory status. The intended use of a product can be determined several ways. First, advertising or labeling of a product is an obvious means to determine its intended use. Second, claims made by the product, such as its use in treating a disease, may establish the product as a drug, even if it is marketed as a cosmetic. An example of this would be an antiperspirant deodorant. Deodorants alone are applied to the body to help cover up body odor associated with bacterial breakdown of perspiration. An antiperspirant has a drug-like action in not only affecting odor but also preventing sweat by affecting the pores. This falls under the definition of “affecting the structure or function of the body.” Therefore, a plain deodorant without an antiperspirant may be classified as a cosmetic, but when the antiperspirant is added, it changes the classification of the deodorant to a drug. Lastly, the active ingredient of the product can be used to classify it as either a cosmetic or drug. As mentioned previously, this concept may come into play should a compound contain an SPF. The SPF component may alter the cosmetic to be seen with drug-like actions. Advertising of SPF within a product is subject to regulations and should be evaluated by the pharmacist.

Cosmetics, by law, are required to be safe. However, there is no regulation requiring cosmetic manufacturers to test for safety (although the FDA strongly encourages testing of products for safety). If a cosmetic product is not tested for safety, the product must bear the warning, “the safety of this product has not been determined.” Cosmetic manufacturers are also only subject to voluntary registration with the FDA (drug manufacturers are required to register with the FDA). The labeling of drugs and cosmetics also differs in that drug labels must only list the active ingredients, whereas cosmetics must list all ingredients in descending order of concentration, with the exception of those ingredients comprising <1 percent of the total product.

CONCLUSION

Many pharmacists have recognized the need for customized compounded products and are interested in performing this type of service, yet are unsure of how to begin. Starting slowly, and offering a customized line of products for a particular disease state will help a compounding practice to grow. The dermatologic disease states covered in this article are excellent starting points for compounded prescriptions due to their prevalence and demand for customized products. As dermatologic compounding, especially of cosmeceuticals, encompasses a much larger realm than what can be expected to be covered in this article, interested pharmacists should use the resources listed above to explore this area further. While there are opportunities for compounding cosmeceuticals, the pharmacist must be prudent in ensuring compliance with all legalities.

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For the list of references used in this article, please contact America’s Pharmacist Managing Editor Chris Linville at 703-838-2680, or at chris.linville@ncpanet.org.
CONTINUING EDUCATION QUIZ
Select the correct answer.

Use the following case to answer questions 1–4. A 13-year-old pubescent male presents to the pharmacy with a mild case of facial acne. Upon examination you discover that he has approximately 15 open and closed comedones on the t-zone of his face, with mild inflammation present.

1. Assuming the patient has not yet tried any OTC agents, what would be an appropriate OTC first line agent to treat his acne?
   a. Benzoyl peroxide
   b. Sulfur
   c. Salicylic acid
   d. Glycolic acid

2. Based on this patient’s presentation, what causative agent(s) is responsible for his acne breakout?
   a. Increased androgen levels
   b. Increased sebum production
   c. Hypercornification of the PSU
   d. All of the above

3. The patient returns to your pharmacy after two weeks with no signs of improvement in his acne. He presents you with a prescription from his dermatologist. What would be an appropriate initial prescription treatment for this patient?
   a. Oral spironolactone
   b. Monotherapy with topical clindamycin
   c. Topical tretinoin cream
   d. Oral isotretinoin

4. Which statement regarding application of topical acne agents is correct?
   a. Topical tretinoin should be applied first thing in the morning.
   b. A patient with hyperirritable skin should use a gel as opposed to a cream formulation.
   c. Topical adapalene should not be used at the same time as benzoyl peroxide.
   d. Benzoyl peroxide may be used as monotherapy or in combination with antibiotics.

5. Which of the following statements regarding the pathophysiology of acne is true?
   a. Due to the association of increased hormone levels and acne prevalence, current guidelines recommend routine endocrinologic assessments for patients presenting with acne.
   b. Sebaceous glands are not found on the back or upper, outer arms; therefore, acne is not common in these areas.
   c. An open comedone is otherwise known as a blackhead.
   d. *P. Acnes* is only found in patients experiencing an active acne breakout.

6. True or False: a 2-year-old with bilateral scaly rashes on the cheeks without pruritis is presenting with atopic dermatitis.
   a. True
   b. False

7. Which of the following is considered first line in treatment of atopic dermatitis?
   a. Avoidance of irritants/allergens
   b. Immunomodulators
   c. Oral antibiotics
   d. Non-sedating antihistamines

8. Which of the following would be an appropriate nonpharmacologic recommendation to the parents of a child suffering from atopic dermatitis?
   a. Hot baths to soothe the itchiness associated with atopic dermatitis.
   b. Wipe the lesions with an alcohol-based astringent to decrease weeping.
   c. Apply a moisturizing agent to the skin after bathing.
   d. Use powder laundry detergents rather than liquid.
9. Which of the following patients would be most at risk for developing atopic dermatitis?
   a. A 36-year-old female with a family history of osteoporosis
   b. A 4-year-old male child with a family history of asthma
   c. A 10-year-old female child who lives in a rural area
   d. An 80-year-old male with seasonal allergies since the age of 5

10. Which of the following agents would be appropriate for inclusion into a moisturizer compounded for a patient with atopic dermatitis?
   a. Propylene glycol
   b. Lactic acid
   c. Sulfur
   d. Tacrolimus

11. M.F. is a 52-year-old female who is concerned about signs of aging. Which of the following factors could have attributed to the aging phenomenon in this patient?
   a. Decreased melanocytes, resulting in decreased UV light protection
   b. Decreased skin cell turnover, resulting in dry skin cells
   c. Cartilage and bone loss with advanced age
   d. All of the above

12. Which of the following cosmeceutical ingredients has both exfoliating and moisturizing properties?
   a. Coenzyme Q10
   b. Ferulic acid
   c. Alpha hydroxyl acids
   d. Hydroquinone

13. A patient presents with UV post-inflammatory hyperpigmentation. Which of the following ingredients would be appropriate to add to a cosmeceutical compound to treat this condition?
   a. Morinda citrifolia
   b. Hydroquinone
   c. Ferulic acid
   d. Vitamin E

14. Which of the following statements regarding skin hyperpigmentation is true?
   a. Solar lentigines are most common in a younger population (<35 years) exposed to UV radiation.
   b. Freckles tend to increase in number with increasing age.
   c. Freckles are unilaterally distributed on the face and trunk.
   d. Lentigines are more common in males.

15. K.P., a 37-year-old female, presents to the pharmacy with hyperpigmentation of the face. It appears to be bilaterally distributed. Her current medications are as follows:

<table>
<thead>
<tr>
<th>Medication</th>
<th>Directions</th>
<th>Start Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrochlorothiazide 25 mg</td>
<td>1/2 tab QD</td>
<td>08/15/2007</td>
</tr>
<tr>
<td>Calcium carbonate 500 mg</td>
<td>1 tab TID</td>
<td>02/04/1996</td>
</tr>
<tr>
<td>Ortho Tri-Cyclen Lo</td>
<td>1QD</td>
<td>06/11/2006</td>
</tr>
</tbody>
</table>

K.P had a child five years ago and has no other significant family or social history. What is the most likely cause of her facial hyperpigmentation?
   a. Melasma
   b. Café-au-lait spots
   c. UV-induced hyperpigmentation
   d. Diabetic dermopathy

16. True or False: The FDA categorizes “cosmeceuticals” as a sub-category of drugs and medical devices.
   a. True
   b. False
17. The role of fluoride is to prevent tooth decay by promoting tooth remineralization. A toothpaste containing fluoride would then be classified as what according to the FDA?
   a. Cosmetic
   b. Food
   c. Drug
   d. None of the above

18. True or False: Like drugs, cosmetics are regulated by the FDA.
   a. True
   b. False

19. Which of the following patient(s) would benefit from a custom-compounded medication?
   a. An elderly patient on multiple high-dose medications
   b. Pediatric patients in need of special dosage delivery forms
   c. Patients with unique medical conditions
   d. All of the above

20. When determining whether a cosmeceutical is a drug or cosmetic, which of the following criteria can be used to determine its intended use?
   a. By using the FDA website
   b. The way that the product is labeled or advertised to the public
   c. Referring to the state board of pharmacy’s discretion
   d. The Personal Care Products Council

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Store e-mail (if avail.): ___________________________
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Quiz: Shade in your choice

1. a b c d e
2. a b c d e
3. a b c d e
4. a b c d e
5. a b c d e
6. a b c d e
7. a b c d e
8. a b c d e
9. a b c d e
10. a b c d e

Quiz: Circle your choice

21. Is this program used to meet your mandatory C.E. requirements?
   a. yes b. no
22. Type of pharmacist: a. owner b. manager c. employee
23. Age group: a. 21–30 b. 31–40 c. 41–50 d. 51–60 e. Over 60
24. Did this article achieve its stated objectives?
   a. yes b. no
25. How much of this program can you apply in practice?
   a. all b. some c. very little d. none

How long did it take you to complete both the reading and the quiz? ______ minutes

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