[LITERATURE REVIEW]

Over-the-counter Acne Treatments
A Review

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ABSTRACT

Acne is a common dermatological disorder that most frequently affects adolescents; however, individuals may be affected at all ages. Many people who suffer from acne seek treatment from both prescription and over-the-counter acne medications. Due to convenience, lower cost, and difficulty getting an appointment with a dermatologist, the use of over-the-counter acne treatments is on the rise. As the plethora of over-the-counter acne treatment options can be overwhelming, it is important that dermatologists are well-versed on this subject to provide appropriate information about treatment regimens and potential drug interactions and that their patients see them as well-informed. This article reviews the efficacy of various over-the-counter acne treatments based on the current literature. A thorough literature review revealed there are many types of over-the-counter acne treatments and each are designed to target at least one of the pathogenic pathways that are reported to be involved in the development of acne lesions. Many of the key over-the-counter ingredients are incorporated in different formulations to broaden the spectrum and consumer appeal of available products. Unfortunately, many over-the-counter products are not well-supported by clinical studies, with a conspicuous absence of double-blind or investigator-blind, randomized, vehicle-controlled studies. Most studies that do exist on over-the-counter acne products are often funded by the manufacturer. Use of over-the-counter acne treatments is a mainstay in our society and it is important that dermatologists are knowledgeable about the different options, including potential benefits and limitations. Overall, over-the-counter acne therapies can be classified into the following five major groups: cleansers, leave-on products, mechanical treatments, essential oils, and vitamins. (*J Clin Aesthet Dermatol.* 2012;5(5):32–40.)

Acne vulgaris (AV) affects nearly everyone at some point in life. Each year, AV continues to be one of the top three dermatological disorders encountered in outpatient dermatological practice, historically affecting mainly teenagers and late preteens. However, the prevalence of adult AV is increasing, especially in women 25 years of age or older. Approximately 81 to 95 percent of adolescent boys and 79 to 82 percent of girls are affected, compared to 3 and 12 percent of adult men and women, respectively.[1] Despite prevalence of AV being highest among adolescents, the mean age of presentation to a physician for treatment is 24 years of age, with the average age of the patient enrolled in clinical trials.[2] There are approximately 45 million people affected by AV in the United States. In 2001, the healthcare expenditure of AV was estimated to exceed one billion dollars.[3]

While overall sales of prescription acne medications have decreased over recent years, there has been an increase in sales of over-the-counter (OTC) acne treatments. Different products line the shelves of pharmacies and department stores around the country, with many advertising that they are "dermatologist recommended." One popular OTC acne kit (Proactiv®), marketed as a treatment system, was projected to generate over 800 billion dollars in revenue in 2010.[4] An impressive marketing strategy and celebrity endorsements have made Proactiv® one of the most popular skincare lines of all time. Most OTC acne treatments are not supported by the same level of global media exposure, marketing dollars, or "pop culture power." Nevertheless, sales of OTC treatments for AV continue to grow because of lower immediate "out-of-pocket" cost compared to prescriptions, outcome promises made within certain marketing or promotional efforts, convenience, the desire to find that one special acne product or treatment program that clears acne quickly, and/or difficulties with access to dermatology practices. Sometimes these access difficulties

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are related to "gatekeeper" roadblocks associated with certain insurance plans. Other times, they are related to long appointment "wait times," especially in some geographic communities.

Commonly referred to as "cosmeceuticals," OTC acne treatments come in lotions, creams, washes, kits, scrubs, brushes, and devices. Due to the sheer number of different OTC brands, plus newer products constantly being developed, it is hard for both physicians and patients to keep abreast of the numerous products. However, all treatments for AV are theoretically designed to target one or more of the pathogenic pathways involved in the development of AV lesions. The conventional breakdown of these pathways includes 1) increased sebum production, 2) abnormal follicular keratinization (microcomedo formation), 3) proliferation of *Propionibacterium acnes*, and 4) inflammation.[5] Hyperkeratinization and increased sebum production creates the perfect environment for proliferation of *P. acnes* early in the pathogenesis of AV. *P. acnes* is a commensal facultative anaerobic bacterium that stimulates an innate immunological cascade and also exhibits several pro-inflammatory properties, with reduction in *P. acnes* colony counts correlating with clinical improvement. Both subclinical and visible inflammation in AV develops with or without follicular rupture, with superficial inflammatory acne lesions developing often without preceding follicular wall rupture. However, in the presence of follicular wall rupture of an obstructed pilosebaceous follicle, which has already been "jump started" to form an AV lesion , the spilling of follicular contents (i.e., sebum, keratin, hair, bacteria) into the dermis leads to deeper inflammation that is essentially akin to a "foreign body reaction" (inflammatory response) to those follicular contents invading the dermis. In this scenario, the visible counterparts of this "dermal intrusion" are more deeply seated inflammatory papules, pustules, and nodules.[6]

OTC acne therapies can be classified into the following five major categories: 1) cleansers, 2) leave-on products, 3) mechanical treatments, 4) essential oils, and 5) vitamins. In this article, cleansers and leave-on products are discussed together as they often contain similar active ingredients, such as benzoyl peroxide, salicylic acid, and others. Physicians, particularly dermatologists, are encouraged to be well-versed in OTC acne treatments to provide appropriate information about their treatment regimen and potential interactions with prescription treatments. The dermatologist who is knowledgeable in all treatments for AV, including OTC products, and who does not present a judgmental attitude regarding their previous use, is more likely to be perceived by patients as more interested in assisting them, thus augmenting their professional validity in the eyes of their patients.

CLEANSERS AND LEAVE-ON PRODUCTS

True soaps and synthetic detergents. Cleansing is a large part of personal health and hygiene, resulting in removal of unwanted dirt, bacteria, and dead skin cells, which theoretically should allow for better percutaneous penetration of topical drugs/medications.[7] When soap was first developed many years ago, it was used mainly for cleansing purposes, but over the decades, the function of skin cleaners, which has progressed beyond true soaps, has morphed to encompass both health and cosmetic benefits. Over time, true soap has evolved into much more than a cleansing agent, with synthetic detergents (syndets) used in both bar and liquid cleansers demonstrating lessened skin irritation. As a result, non-soap-based skin cleansers are now marketed to decrease aged appearance of skin, soften skin, and improve overall skin health.

By definition, a true soap is a salt made of an alkali and a fatty acid; the alkali either consists of sodium or potassium hydroxide with pH ranging from 9 to 10, which is markedly more alkaline than the natural "acid mantle" of the epidermis.[8] Daily use of a true soap compromises the permeability barrier of the stratum corneum (SC), resulting in damage to the intercellular lipid bilayer and SC proteins, both of which contribute to regulation of transepidermal water loss (TEWL) and SC hydration necessary for normal desquamation and prevention of xerosis.

Synthetic surfactants are the major ingredient in syndets; other ingredients include high-melting-point fatty acids, waxes, and esters. Due to the unique molecular properties of the surfactants, syndets are incorporated in the mildest bar and liquid cleaners available in the marketplace. Some incorporate lipid-based technologies, such as incorporation of free fatty acids for replenishment and optimal surfactant selection to reduce damage to integral SC proteins.

In a randomized, double-blind study by Subramanyan et al,[7] patients undergoing topical acne treatment were randomly assigned to use either a soap or syndet bar (N=25). The syndet bar group demonstrated a greater reduction in signs and symptoms of cutaneous irritation and some decrease in AV lesions compared to the group using soap.[7] In another study by Korting et al,[9] adolescents and young adults were randomized to wash with either conventional true soap or a syndet bar for three months duration (N=120). Results of this study showed an increase in inflammatory AV lesions in the group using conventional soap and a decrease in inflammatory AV lesions in the group using the syndet bar ($p<0.0001$). The authors of this paper hypothesized that use of the true soap increased the pH of the skin leading to a more favorable environment for proliferation of *P. acnes*.[9]

Since the skin has an acidic pH of 5.3 to 5.9, washing the skin with true soap can increase the pH by 1.5 to 2.0 units for 4 to 8 hours. The increase in pH contributes to amplifying TEWL, thus leading to production of visible changes of dryness. In addition, the increase in pH may facilitate microbial growth potentially leading to increase in *P. acnes* and development of AV lesions.[10,11] The pH of syndet cleansers hover around 5.5 and do not modify the pH of the skin.[12]

As an alkaline pH can also impair enzymes involved in normal SC functional integrity, true soaps contribute to xerotic changes within skin leading to fine fissuring, scaling, and sometimes low-grade inflammation, which produces

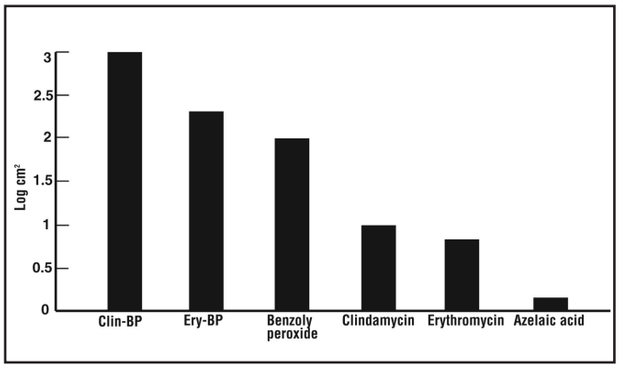

Figure 1. Reduction of *Propionibacterium acnes* with topical therapies. Reprinted with permission from: Leyden JJ. Current issues in antimicrobial therapy for the treatment of acne. *J Eur Acad Dermatol Venereol.* 2001;15(Suppl 3):51–55.

erythema. With regard to AV, these adverse xerotic changes may potentiate cutaneous irritation associated with some topical acne medications, such as retinoids and/or benzoyl peroxide. On the other hand, use of a syndet-based skin cleanser can reduce the potential for cutaneous irritation that is sometimes associated with topical therapies for AV.

Benzoyl peroxide. Benzoyl peroxide (BP) is an organic acid in the peroxide family that has been a fundamental component of therapy for AV for more than six decades. In addition, BP is used for a variety of other purposes (i.e., hair/teeth bleaching, preparation of flour, polymerization reactions). Since the 1930s, BP has been a popular choice for the treatment of AV due to its keratolytic, moderate comedolytic, and antibacterial properties, which include the reduction of *P. acnes* and *Staphylococcus aureus* on skin.[13,14] Cutaneous side effects of BP are most often irritant in nature, may be concentration and/or vehicle dependent, and are usually mild, including signs such as dryness, erythema, and fine scaling. A minority of the population treated with BP for AV will experience true allergic contact dermatitis (1:500). Although available OTC, BP is a pregnancy category C agent, suggesting that its use in pregnancy may not be prudent.

Common use worldwide of topical and oral antibiotics for treatment of AV over the past 3 to 4 decades has led to an increase in *P. acnes* strains that are less sensitive to antibiotics that are commonly used for treatment of AV, especially erythromycin and tetracycline. When the *in-vitro* mean inhibitory concentration of a specified antibiotic increases to predetermined breakpoints, the tested *P. acnes* strain is determined to be "resistant" to that antibiotic, with relative rates of high-level and low-level *P. acnes* resistance reported in some studies. Global rates for the presence of antibiotic-resistant *P. acnes* strains, most often highest to erythromycin followed by tetracycline, rose from 20 percent in 1978 to 62 percent in 1996. Resistance is most common with erythromycin, clindamycin, and tetracycline; however, reported rates with doxycycline, trimethoprim, and minocycline have increased in direct correlation with geographic usage patterns.[15]

When BP is combined with a topical antibiotic (i.e., erythromycin, clindamycin), there is an augment antibacterial effect based on log reductions of *P. acnes* in addition to a decrease in the emergence of both new and pre-existing antibiotic-resistant *P. acnes* strains.[16] Combination gel formulations of BP with erythromycin or clindamycin are only available by prescription in the United States. BP is equally effective against erythromycin-sensitive and erythromycin-resistant *P. acnes* and coagulase-negative *S. aureus in vitro*.[16] Clinical studies have shown that the combination gel formulations of BP and erythromycin or BP and clindamycin are more effective than either active agent used as monotherapy in decreasing acne lesions, especially inflammatory lesions (Figure 1).[13,15,17] The effectiveness of the topical antibiotic and BP may be explained by their independent antibacterial effects, the moderate comedolytic effect of BP, and potentially anti-inflammatory properties associated with erythromycin or clindamycin, although the latter are not as well defined.[13]

Available OTC, BP-based products for AV range in concentration from 2.5 to 10% and encompass a wide variety of vehicle formulations. In three double-blind studies of patients with mild-to-moderately severe acne vulgaris, 2.5% BP gel was compared to its vehicle and also to 5 and 10% BP gel preparations (N=153).[18] The results showed the 2.5% BP was more effective than its vehicle and equivalent to the 5 and 10% BP preparations. Cutaneous side effects, such as desquamation, erythema, and burning, were increased with the higher concentration formulas.[18] Therefore, BP concentrations greater than 2.5% do not necessarily increase the efficacy of treatment in patients with facial AV. However, higher concentrations may be associated with increased risk and severity of signs and symptoms of application-site irritation. In addition, efficacy, tolerability, safety, and microbiological data on OTC formulations of BP have not always been completed and/or are not often published. As a result, it is difficult for the practicing clinician to make specific BP product recommendations to patients based on clinical and scientific evidence. This latter issue is confounded by the recent mandate from the United States Food and Drug Administration (FDA) directing that all BP formulations be available OTC, including those currently available by prescription only. All such formulations are given a basic designated BP monograph that is ascribed to the product ("class labeling"), although each specific product has not been studied individually in support of all of the information included in the designated monograph.

BP is also available by prescription. To the authors' knowledge, there are no published direct-comparison ("head-to-head") trials comparing OTC BP formulations to prescription BP formulations. However, some prescription formulations contain additional ingredients, which may decrease irritation and enhance delivery, and many are supported by published clinical trials evaluating clinical efficacy, primarily for facial AV, and/or microbiological data

evaluating *P. acnes* reduction.

A six-week clinical study by Sawleshwarkar et al[19] examined the efficacy and tolerability associated with a 4% BP cream in a hydrophase base (Brevoxyl®, Steifel Labs, Research Triangle Park, North Carolina) that was until recently available only by prescription.[19] Results showed that the BP 4% cream was efficacious and well tolerated.[19] The hydrophase vehicle, which contains dimethyl isosorbide (DMI), produces dissolution of BP which is believed to reduce irritation that can occur with BP. Many formulations incorporate BP crystals that vary in size and do not necessarily fully dissolve completely or at the same rate. Larger crystals that are not capable of settling into the follicular ostia due to their size may randomly rest on the skin surface for more prolonged periods of time, thus producing scattered foci of "hot spots" that may present as patches of cutaneous irritation.

TABLE 1. Characteristics of alpha-hydroxy acids and beta-hydroxy acids

HYDROXY ACID	SOLUBILITY	SOURCE	PENETRATION	ACTION
Alpha-hydroxy acid	Water soluble	—	Dermis (at high concentrations)	Exfoliative
Glycolic acid	—	Sugar cane	—	—
Lactic acid	—	Sour milk	—	—
Beta-hydroxy acid	Lipid soluble		Epidermis and pilosebaceous unit	Exfoliative, comedolytic, anti-inflammatory
Salicylic	—	Willow bark, wintergreen, sweet birch	—	—

Hydroxy acids. Hydroxy acids can be divided into two major categories: α-hydroxy acids (AHA) and β-hydroxy acids (Table 1). Both AHA and β-hydroxy acids are used for cosmetic applications in dermatology but differ in their structures and chemical properties. AHAs are a group of chemical compounds that have a carboxylic acid moiety that is substituted with a hydroxyl group at the α position of the acid, which confers water solubility to the compound. Whereas, lipid-soluble β-hydroxyl acids are a group of chemicals containing a carboxyl and hydroxyl group separated by two carbons atoms, making the compound lipid soluble.

α-*hydroxy acids (AHA).* AHA's are a group of hydroxy acids including glycolic, lactic, and citric acid. The exact mechanism of action of AHAs is not completely understood. They exert some effect by thinning the stratum corneum, promoting epidermolysis, dispersing basal layer melanin, and increasing collagen synthesis within the dermis.[20] A study conducted by Ditre et al[21] showed patients that applied 25% glycolic, lactic, or citric acid for six months had an approximately 25-percent increase in both epidermal and dermal thickness. Histological staining demonstrated increased mucopoly-saccharides, improved quality of elastic fibers, and increased density of collagen.[21]

Hyperkeratinization (hyperkeratosis), subclinical, clinical, or both, often results secondary to abnormal SC desquamation and epidermal thicken-ing, both often responses to impairment of the SC permeability barrier. With loss of cutaneous hydration, the decrease in mechanical resiliency of the epidermis leads to microfissuring and often to visible skin splits (macrofissures), the latter being fine and superficial (eczema craquele) or discrete and deep (canyon-like fissures of hyperkeratotic hand-foot eczema or keratoderma). Hyper-keratinization may be acquired or may be inherent to the progression of a variety of underlying skin disorders that are focally or diffusely involved in the progression of many common skin diseases including AV, eczematous dermatoses, severe xerosis, plaque psoriasis, and verrucae. Histologically, hyperkeratinization presents as a thickened SC and is sometimes associated with epidermal thickening. At lower concentrations, AHA functions as an exfoliant, interrupting corneocyte adhesion in the upper SC by interfering with formation of ionic bonds. As a result, AHAs promote individual corneocyte desquamation and decrease corneocyte clumping, both of which lead to smoother skin texture and decreased visible scaling and flaking; a decrease in follicular hyperkeratois promotes resolution and prevents formation of AV lesions, especially comedones.[22,23] Higher concentrations of AHAs (8–10%) can lead to both epidermolysis and thickening of the dermis.

Brief exposure to glycolic acid at concentrations of 30 to 70 percent is frequently used in superficial peeling, which may serve as an effective adjunct in patients with multiple and/or persistent closed comedones.[23]

β-*hydroxy acids*. Salicylic acid, the only β-hydroxy acid that is used in dermatological practice, is lipophilic, and is a very common active ingredient in a plethora of OTC acne cleansers, astringents, and lotions. Due to its desmolytic properties, salicylic acid promotes individual corneocyte desquamation, thus simulating natural exfoliation, and exerts moderate comedolytic activity. The desmolytic and comedolytic properties of salicylic acid are concentration-dependent. In fact, salicylic acid is not keratolytic. Rather, it exerts its effect on SC desquamation by breaking the bonds created by corneodesmosomes, also called the "rivets" or "staples" of the SC, which sustain the adherence between contiguous corneocytes.[23] As a result, mild visible peeling may be noted, and some salicylic acid-containing vehicles may promote cutaneous irritation, while others (i.e., multivesicular emulsion, emollient foam) are associated with little-to-no skin tolerability reactions.

OTC salicylic acid acne treatments include con-

centrations of 0.05% to 5%. Higher concentrations are reserved for salicylic acid prescription medications and chemical peels. The "physiological" desquamation provided by salicylic acid provides smoother texture and appearance to the skin and can give the illusion of decreased pore sizes. Unfortunately, lower concentrations of salicylic acid may provide only a modest desmolytic activity, thus producing minimal therapeutic effects.

A 12-week, double-blind, randomized study by Shalita et al[24] evaluated the response of mild-to-moderate AV with use of Stridex® pads (0.5% salicylic acid, Blistex, Oak Brook, Illinois) twice daily as compared to patients using vehicle pads twice daily, both applied twice a day for 12 weeks. The actively treated group demonstrated greater reduction of both inflammatory lesions and open comedones.[24]

Kessler et al[25] compared the efficacy of α- and β-hydroxy peels in the treatment of mild-to-moderately severe facial AV in a split-face, double-blind, randomized, controlled study. Twenty patients were recruited to the study; a α-hydroxy (30% glycolic acid) was applied to one half of the face and a β-hydroxy (30% salicylic acid) to the contralateral side every two weeks for a total of six treatments. There was no significant difference in efficacy between the two peels; however, salicylic acid had fewer initial side effects and sustained effectiveness at two months after treatment.[25]

Hydroxy acids are categorized as pregnancy category C; animal studies demonstrate birth defects when given orally in doses six times the maximum topical dose. Salicylism, although rare, can occur, especially in patients with impaired stratum corneum permeability barrier function receiving treatment over a large body surface area.[26]

Polyhydroxy acids (lactobionic acid and gluconolactone). Polyhydroxy acids (PHA), the new generation of AHAs, provide similar effects of traditional AHAs without the associated sensory side effects of irritation and stinging.[27] PHAs are formulated as multiple strand molecules allowing for slower and gentler absorption rate, reducing aforementioned side effects, making them compatible for use on clinically sensitive skin.[28]

One PHA, lactobionic acid, has been suggested to be an inhibitor of the breakdown of matrix metalloproteinase enzymes (MMPs), possibly due to metal chelation. Breakdown of these MMPs due to sun exposure contribute to the appearance of photoaging. Lactobionic acid is a strong metal chelator conferring antioxidant properties; it is currently used as an antioxidant in organ transplantation. Additionally, PHAs have strong moisturizing and humectant properties.[28] The combination of PHAs and tretinoin has been shown to decrease the total number of acne lesions and both subjective and objective measures of irritation.[28]

Triclosan/triclocarban. Triclosan/triclocarban are bacteriostatic agents that can be found in a variety of household items and are often the key ingredient in OTC acne cleansers and washes. Triclosan is a bisphenol disinfectant, with action against gram-positive and most gram-negative organisms and is used in surgical scrubs/soaps and deodorants.[29] However, topical antibiotics should never be used as monotherapy and are preferably combined with other topical nonantibiotic antimicrobials such as benzoyl peroxide.[30]

MECHANICAL TREATMENTS

Scrubs. Abrasive scrubs came to fruition after the anecdotal observation that desquamation of the SC can lead to younger, smoother-appearing skin. Scrubs may contain different types of abrasives, such as polyethylene beads, aluminum oxide and ground fruit pits, or sodium tetraborate decahydrate granules.[31] The theoretical rationale behind the use of scrubs for acne treatment is that the abrasion may unroof closed comedones and prevent their progression.[32] However, the irritant effects and/or damage to SC functional integrity caused by physical abrading caused by scrubbing must be considered, as this is likely to augment the potential for cutaneous irritation that may be associated with topical acne therapies.

Because of their irregular shape, the most abrasive scrubs are those containing ground fruit pits and aluminum oxide. These are not recommended for patients with sensitive skin. Scrubs containing sodium tetraborate dechydrate granules dissolve during washing, making them the least abrasive.[31]

Cleansing cloth (nonwovens, towelettes). Cleansing cloths offer a less abrasive cleansing alternative in addition to providing conditioning and exfoliation in a simple application process. The cloths come in the following two forms: 1) cloths that lather, requiring wetting before and rinsing afterwards and 2) moist cloths that do not requiring rinsing after use. Most wipes tend to be mild because of the low surfactant content and also have the additional benefit of increased deposition of active ingredients onto the skin.[8]

Cloths are made of polyester, rayon, cotton, and cellulose fibers, which are joined together by a heating process known as thermobonding. The cloths are then saturated with cleanser that foams modestly when moistened. Humectants and emollients can also be added to the cloths, providing properties designed to counter damage to the SC in addition to cleansing.

The type of cleanser added to the cloth plays an important role in the effect it has on sebum removal and ultimately its role in the treatment of acne vulgaris. The type of weave (open vs. closed) also plays a role in the cutaneous effects of the cloth. Open weave fibers are more conducive to dry, sensitive skin. These open cloths have 2 to 3mm windows between the adjacent fiber bundles, thus decreasing surface contact with the skin while increasing the softness of the cloth providing a more gentle exfoliative effect. In contrast, the closed fiber cloths have a tighter weave and subsequently exhibit a greater exfoliative effect.[31]

The newest generation of cloths now incorporates formulations of BP, salicylic acid, and hydroxy acids in addition to cleansers. A BP containing cleansing cloth has several desirable characteristics compared to conventional 4 or 6% BP wash, including convenience, portability and cosmetic elegance.[33]

Cosmetic adhesive pads. Developed to remove adherent corneocytes, dirt, oil, or loose open comedones from the skin surface, adhesive pads can be used to remove

keratotic plugs (comedones) from the follicular orifices. Biore® (Kao Brands Company, Cincinnati, Ohio) pore strip is a commercially available adhesive pad, onto which a cationic adhesive polymer is deposited. Comedones (follicular plugs) contain anionic amino acids that are attracted to the cationic adhesive polymer; the active agent polyquaternium 37 purportedly binds to comedonal plugs facilitating their extraction on removal of the adhesive pad.[34]

Biore® Pore Strips are applied weekly to wet skin and allowed to harden before being peeled off. For optimal results, it is recommended not to use them more often than once every three days. No studies have been conducted looking at the efficacy of Biore® Pore Strips in the treatment of AV, but they have been reported in the treatment of trichostasis spinulosa.[34]

Brushes. Developed by the makers of the Sonicare® toothbrush, Clarisonic® (Pacific Life Bioscience, Bellevue, Washington) skin care brush is one of the most commonly found OTC skin brushes. Although not marketed for treating AV, many acne sufferers will inquire about this product due to the popular myth that unclean skin may cause AV. The Clarisonic® skin care brush has an oscillating motion that deeply cleanses the skin while removing makeup. Industry studies have shown Clarisonic® sonic cleansing is twice as effective in cleansing the skin compared to washing with soap and water. In addition, Clarisonic® sonic cleansing is reportedly six times better at removing mineral makeup than manual cleansing.[35] However, the impact of this approach in skin cleansing has not been adequately evaluated

Heating devices. Zeno® (Zeno Corporation, Houston, Texas) is an electronic heating device marketed to treat AV by directly contacting the lesion. The device heats to 121°F. The company claims that the heat "activates heat shock proteins of *P. acnes* causing the bacteria to be killed." Treatment protocol is two to three treatments for 2.5 minutes each over a 24-hour time period.[36] The No!No! Skin® (Radiance, Inc., Orangeburg, New York) is an electronic device postulated to treat acne through heat and phototherapy.

ESSENTIAL OILS

Tea tree oil. Australian tea-tree oil comes from trees of the *Melaleuca* genus; the most common species used is *Melaleuca alternifolia*.[37] Tea tree oil has been used medicinally for approximately 70 years, including for furunculosis and vaginal infections, due to its broad antimicrobial and antifungal properties.[38–40] *Staphylococcus aureus* and most gram-negative bacteria are reported to be sensitive to tea tree oil. Terpinen-4-ol is considered the active ingredient of tea tree oil, but studies have shown alpha-terpineol and alpha-pinene also have intrinsic antibacterial properties.[37] One comparison of tea tree oil and BP for treatment of mild-to-moderate acne revealed both compounds have similar efficacy, although the onset of action is slower for tea tree oil.[41] A randomized clinical trial compared tea tree oil to a placebo over six weeks in the treatment of AV measuring total lesion count (TLC) and acne severity index (ASI). Tea tree oil was 3.5 times more effective than the placebo in reducing TLC and 5.75 more effective than the placebo in reducing ASI.[42]

Some studies support that tea tree oil has anti-inflammatory activity as well. Terepin-4-ol has been shown in an *in-vitro* study to suppress production of pro-inflammatory mediators by activated human monocytes.[43] Another study demonstrated the water-soluble components, terpinen-4-ol, alpha-terpineol and 1,8-cineole, suppress the production of superoxide by monocytes, but not neutrophils.[44] *In-vivo* studies have demonstrated the ability of terepin-4-ol to modify vasodilation and plasma extravasation associated with histamine-induced inflammation.[45] These anti-inflammatory properties have been suggested to account for its potential usefulness in treating AV; however, the role of this pathway of inflammation in the pathogenesis of AV has not been defined.

Although tea tree oil may be beneficial, it can also induce allergic contact dermatitis. It has been proposed that photo-oxidized products from poor storage conditions are the cause of allergic reactions.[46,47] One study found the risk of developing allergic contact dermatitis induced by tea tree oil was less than one percent.[48]

VITAMINS AND THEIR ANALOGUES

Retinol. Retinoids are a biologically active group of compounds derived from vitamin A existing as both natural and synthetic derivatives.[49] These compounds play important roles in biological/physiological functions including vision, tissue maintenance/differentiation, glycoprotein synthesis, growth, and hematopoesis. Retinoids increase cell proliferation; however, paradoxically they have a normalizing effect in hyperproliferative epithelium as they stimulate epithelial differentiation.[49]

All-trans-retinol (ROL) is the predominant retinoid in circulation. It binds to either of two nuclear receptors in the keratinocyte, the retinoic acid receptor (RAR) and the retinoid X receptors (RXR), thus activating retinoid hormone response elements (HREs) where transcription is regulated. Retinoid HREs activate genes responsible for the normalization of keratinization and decreasing the cohesiveness of keratinocytes reducing development of microcomedones.[50] Other dermatological effects of vitamin A derivatives act through changes in cellular proliferation and differentiation, inflammation, and sebum production, the latter dependent on the specific compound and route of administration. Topical retinoids available in the United States have not been shown to inhibit or increase sebum production.

Retinol appears to exhibit greater cutaneous penetration than tretinoin. Retinol 0.25% may induce cellular and molecular changes observed with tretinoin 0.025%. Although retinol is less potent pharmacologically than tretinoin, it produces less skin irritation and erythema overall, and unlike tretinoin, has not been adequately evaluated for treatment of AV.[51–53] Consumers must be aware that not all products containing retinol have the same

concentration and/or formulation characteristics.

Zinc. Zinc is an essential trace element necessary for the survival of animals, plants, and micro-organisms. This metallic chemical element is found in more than 100 enzymes and serves as structural ions in transcription factors. The 2 to 4 grams of zinc distributed throughout the human body plays a role in the metabolism of ribonucleic acid (RNA)/deoxyribonucleic acid (DNA) signal transduction and gene expression.

The role of zinc salts in treatment of AV has not been fully explicated; however, the use of these salts has been routine since the 1970's in topical acne therapies. It is known that zinc salts have an anti-inflammatory effect mediated by the inhibition of chemotaxis in acne patients. In addition, zinc salts have the potential to decrease the release of inflammatory cytokines, increase superoxide dismutase activity, modulate the expression of integrins and inhibit Toll-like receptor-2 surface expression on keratinocytes, and have a sebosuppressive effect.[54,55]

A large, multicenter, randomized, double-blind, controlled, clinical trial compared oral zinc gluconate versus oral minocycline in the treatment of inflammatory acne. It was found that although both were effective treatments in inflammatory acne, minocycline had a superior effect after one month.[56] However, zinc can be an alternative treatment for pregnant women because of its safety profile, and it is not associated with side effects, such as vertigo or hyperpigmentation. Also, zinc does not cause bacterial resistance and when used in combination with erythromycin it has been shown to preclude the development of erythromycin-resistant strains of P. acnes.[55]

Nicotinamide. Nicotinamide, the water-soluble amide derivative of vitamin B_3 (niacin) is used both orally and topically in the treatment of AV and other inflammatory skin conditions.[57] It has been reported to inhibit cytokine release by keratinocytes and downregulate expression of the interleukin (IL)-8 gene and production of IL-8 protein, which is a focal point in promotion of inflammation. Topical nicotinamide gel 4% has been shown in one study to be as effective as clindamycin gel 1% in the treatment of AV without the development of antibiotic resistance, a factor that is important for patients undergoing treatment for a sustained period of time; however, a more thorough evaluation is needed including assessment based on severity of AV.[58,59]

The Nicomide Improvement in Clinical Outcomes Study (NICOS) evaluated the efficacy of oral pharmacological doses of zinc and nicotinamde in AV and rosacea over eight weeks. The formulation used in the study consisted of nicotinamide 50mg, zinc 25mg, copper 1.5mg, and folic acid 500µg. Improvement in appearance was reported in 79 and >50 percent of patients within the first four weeks of the study. Comparison with concomitant oral antibiotic treatment showed no difference in improvement rendering addition of an oral antibiotic regimen unnecessary. However, this suggestion is not applicable, as use of oral antibiotic therapy for AV without concomitant rational topical therapy is not recommended.[60]

Sulfur. Sulfur is a nonmetallic natural element found abundantly in the earth's crust. It has been shown to exhibit antimicrobial properties and has been used medicinally for hundreds of years, including the treatment of AV. The clinical effects of sulfur in the treatment of AV and seborrheic dermatitis is believed to be due at least partially to its keratolytic effects, thought to be due to the interaction between the keratinocyte and the cysteine component of sulfur.

Sulfur is usually combined with other topical agents, such as BP, salicylic acid, and resorcinol. In OTC acne products, sulfur is usually combined with resorcinol, whereas in prescription formulations it is found in a concentration of 10% in combination with sodium sulfacetamide.[50] Resorcinol is thought to have intrinsic antibacterial, antifungal, and keratolytic activity; however, it is not believed to be effective as monotherapy.[61] Use of sulfur and resorcinol causes mild irritation and sensitization.[30] In addition, the malodor associated with sulfur products has limited its popularity as an OTC acne product.

DISCUSSION

Many people use OTC acne treatments as their first attempt to treat AV or at different times over their lifetime due to the chronicity of the disorder. In addition to being available at local pharmacies or via the Internet, some ingredients commonly used in OTC acne treatments, such as BP and sulfur, are also available in prescription formulations. Major categories include 1) cleansers/leave-on products, 2) mechanical treatments, 3) essential oils, and 4) vitamins. To further establish the efficacy of OTC acne treatments, well-designed, adequately powered, blinded, randomized, clinical trials are needed to better establish the efficacy and tolerability of OTC products for AV. This is especially important as the FDA mandates that some active agents, such as BP, be designated for OTC use. Unless OTC acne products are supported by appropriate clinical trials, dermatologists and their staff will be without the necessary information essential to appropriately differentiate and recommend OTC products. OTC products may certainly be of benefit for patients; however, lack of good studies to support some OTC products for AV and other disorders creates a challenge for clinicians. Hopefully, manufacturers will step up to the challenge by designing and completing studies that provide clinically relevant that supports the recommendation of their products.

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