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An Algorithm Integrating Acneceuticals Into the Management of Acne Vulgaris

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ABSTRACT

Background: Acne vulgaris is a common, chronic cutaneous disorder with numerous efficacious prescription and procedural treatments. Therapy, however, is hampered by medication intolerability and compromised by non-adherence. The use of acneceuticals is an effective way to improve patient outcomes.

Methods: A panel of 5 dermatologists met for a consensus conference in October 2023 to identify a practical acne treatment and maintenance algorithm integrating acneceuticals with prescription medications and procedures.

Results: The algorithm stratifies the use of acneceuticals first as monotherapy, adjunctive therapy, or maintenance therapy and then further diverges by skin phenotype (oily or dry/sensitive) and primary lesion morphology (comedonal or inflammatory). Finally, specific acneceuticals are recommended for each phenotypic description.

Conclusion: The algorithm is intended to serve as a guideline for integrating active nonprescription skin care into prescription acne therapy, improving efficacy, tolerability, and adherence, resulting in superior patient outcomes.

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INTRODUCTION

Although many quality prescription products exist for the treatment of acne, we continue to search for ways to improve patient care. Our patients search as well, often adding or substituting internet finds for proven regimens, occasionally with deleterious consequences. It is incumbent upon clinicians to be well-versed in ways in which nonprescription active skin care ingredients can improve patient outcomes. It is the clinician's responsibility to guide patients in their quest for self-care, helping them to choose quality products, improve safety and reduce cost.

In a previous study, the results of a modified Delphi consensus meeting were reported where the term "acneceutical" was coined to encompass nonprescription formulations with ingredients efficacious in acne.[1] A thorough literature search resulted in the identification of candidate ingredients that were divided into categories based on the pathophysiology of acne: sebum inhibitors, anti-inflammatory agents, antibacterial agents, keratolytic agents, and those that repair the deficient barrier (Table 1). These candidates were vetted for those that were studied in patients with acne in double or single-blind, vehicle-controlled, or active-compared designs. Combination products and proprietary blends to which patients would not have access were omitted as were benzoyl peroxide and adapalene, viewing them as drugs, not acneceuticals.

In this paper, we present an algorithm incorporating these acneceuticals into acne management as monotherapy, adjunctive therapy (to pharmaceuticals or procedures), and maintenance therapy following discontinuation of prescription medications.

Algorithm Development

The algorithm focuses on integrating acneceuticals into an acne management and maintenance regimen. The algorithm went through numerous iterations as individual acneceuticals were evaluated for quality of data, proposed mechanism of action, and their likely role in acne care. This information guided the panel to crystallize the most salient subdivisions and branchpoints of the algorithm. The panel reviewed and edited the final algorithm in a consensus conference.

TABLE 1.

Mechanism of Action of Acneceuticals in Acne	
Mechanism of Action	**Actives**
Keratolytic	Alpha and beta hydroxyacids Azelaic acid Retinol derivatives Bakuchiol Silymarin Sulfur
Antibacterial	Azelaic acid Niacinamide Zinc Green Tea Resveratrol Silymarin Bakuchiol Soy Probiotics Retinaldehyde Sodium hypochlorite Tea tree oil
Anti-inflammatory	Niacinamide Bakuchiol Salicylic acid Azelaic acid Linoleic acid Lactobacillus Aloe vera Green tea Cannabidiol Zinc Resveratrol Silymarin Sodium hypochlorite Tea tree oil
Sebum reduction	Niacinamide Zinc Green tea Silymarin Bakuchiol Linoleic acid Clay Soy Resveratrol
Barrier repair	Hyaluronic acid Alpha and beta hydroxy acids Glycerin Colloidal oatmeal Niacinamide Panthenol Ceramides Shea butter

The proposed use of acneceuticals was based on an understanding of acne pathophysiology. Acne pathophysiology is traditionally tied to 4 pathogenic pillars: hyperkeratinization, hyper- and dysseborrhea, *Cutibacterium acne* (*C.acnes*) colonization, and a robust inflammatory response.[2,3] Additional data implicates skin barrier impairment as a material contributor to the pathophysiology of acne.[4] Based on these tenets of acne pathophysiology, acneceuticals were chosen for inclusion if they had in vitro or in vivo data indicating mechanisms of action that included keratolysis, inhibition of sebum production, antibacterial activity (specifically against *C. acnes*) and anti-inflammatory activity as well as barrier repair. Many acneceuticals have more than one potential area of efficacy and thus are included in more than one category.

It is well documented that when composing a treatment regimen for acne, combination therapy is the most effective; in particular, utilizing drugs that approach the acne pathogenic cascade from numerous directions.[5,6] It is likely that in clinical practice, we will need to choose several acneceuticals with differing mechanisms of action to maximize efficacy.

The Algorithm (Figure 1)

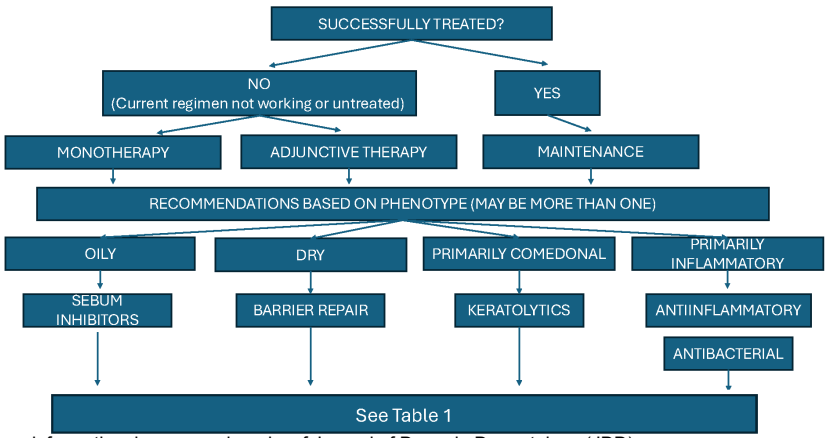
First Stratification

The first stratification of the algorithm is the choice of maintenance therapy for the successfully treated patient and monotherapy, or adjunctive therapy for the patient who needs continued care.

Monotherapy

Several acneceuticals had data demonstrating efficacy in acne as standalone treatments.[1] However, just as with prescription medications, it is expected that in clinical practice, combination therapy will be most effective. Simultaneous use of actives from categories with different mechanisms of action is recommended. Most monotherapy studies were conducted on subjects with mild disease; there is little data evaluating solo

FIGURE 1. Algorithm integrating acneceuticals into the management of acne vulgaris.



agents in patients with more severe disease.[1] It is likely that the use of acneceuticals as adjuncts to prescription medications or procedures will be better suited for more advanced disease.

Adjunctive Therapy

The utilization of acneceuticals for adjunctive therapy has been studied in two ways: the addition of an acneceutical to prescription care to augment effectiveness of therapy and the addition of a barrier repair acneceutical to improve prescription drug tolerability. Acne therapy is often drying, particularly during initial use. Symptoms including itch, sting, and burn can lead to non-adherent behavior and ultimate failure of the regimen.[7-9] Barrier repair has been shown to reduce medication intolerability leading to consistent use of therapeutics and treatment success.[10]

Maintenance (Treatment Transition) Therapy

Treatment transition to alternate regimens is an inevitable necessity in acne care. Once satisfactory lesion clearance has been obtained, patients often become anxious to discontinue all or part of their therapy. As clinicians, we are aware that, with the exception of isotretinoin, acne therapy can best be described as a bandaid on the condition until acne naturally resolves; abrupt discontinuation of efficacious products results in rapid return of disease. Substitution of an appropriate acneceutical – one having the same mechanism of action as the drug itself – may aid in the transition: antibacterial for antibiotic, keratolytic for a retinoid.

Other reasons for treatment transition include cost of and access to medications and tolerability. Acneceuticals, almost without exception, are less expensive than pharmaceutical agents, are accessible to all, without the economic disparity that exists due to affordable access, available for children under the age of FDA approval and highly tolerable.

Lastly, the use of topical and oral antibiotics is associated with the development of antimicrobial resistance. The CDC warns us that antimicrobial resistance is one of the most important public health threats of our time and has called upon us to be better stewards of antibiotics.[11] Although antibiotics are highly effective in reducing *C. acnes* and thus improving inflammatory acne, durability of response is poor. Discontinuation results in inevitable recolonization of the follicle with the commensal *C. acnes* and return of disease, having brought about ecologic damage without ultimate gain. Acneceuticals, with the ability to accomplish microbiome modulation without evident antimicrobial resistance, are a readily available answer to this dilemma, allowing for continued therapy with less risk.

Second Stratification (Figure 1)

The second stratification of the algorithm involves determining the phenotypic description of the patient. Based on the mechanism of action of the acneceuticals, the panel recognized four general phenotypes (realizing that the individual patient will often fall into more than one category): oily skin vs dry/sensitive skin and comedonal vs inflammatory acne. Although acknowledging that maximizing acne therapy is best accomplished by utilizing combination therapy, the panel stratified acneceuticals by determining for which phenotype each was best suited.

Oily Skin

Oily skin patients appreciate products that reduce the appearance of shine in addition to the potential therapeutic benefits that sebum inhibition could accomplish. Sebum excretion is known to be higher in acne patients. Additionally, sebum quality is altered; linoleic acid levels are reduced and squalene concentrations increased, contributing to subclinical inflammation.[12,13] Reduction in sebum excretion is thus an important clinical and cosmetic endpoint that may be accomplished in part by the use of an acneceutical.

Dry and Sensitive Skin

Dry and sensitive skin patients can benefit from barrier repair. Yamamoto and co-workers demonstrated that acne patients have an inherent barrier dysfunction, noting a statistically significant reduction in ceramides and increase in transepidermal water loss.[4] The deficiency was more significant in more severe disease. As barrier dysfunction is known to be accompanied by hyperkeratosis of the follicular epithelium, this suggests that acne should be added to the list of barrier deficiency disorders such as atopic dermatitis and psoriasis. Data suggest that quality skin care may result in acne improvement as monotherapy. We often see this when faced with unexpectedly good results in the vehicle arms of acne studies. Small studies have demonstrated that daily use of a mild facial cleanser and quality moisturizer can reduce acne lesions without aggravating epidermal barrier dysfunction, thereby reducing TEWL, mitigating aberrations of cutaneous pH, and fostering the growth of a diverse and healthy microbiome.[13-15]

In addition to resolving an inherent barrier deficiency, quality skin care improves pharmaceutical tolerability. The acne management paradigm is built on topical retinoids and benzoyl peroxide. Although effective acne drugs, these ingredients also increase cell turnover, induce stratum corneum thinning, and increase TEWL, often leading to xerosis, irritation, and even inflammation. When combined with acne treatment regimens, the use of gentle cleansers and quality moisturizers improves patient comfort, minimizing the adverse effects of dryness and irritation.[14,15] Although there are many factors leading to poor compliance, skin irritation is a prominent factor.[7-9] A double-blinded, randomized study compared the outcome of an acne treatment regimen consisting of a twice-daily skincare routine in addition to a nightly combination topical agent (adapalene

0.3%/BP 2.5%).[10] Use of a ceramide-containing cleanser and moisturizer during the 12-week treatment period resulted in a statistically significant improvement in both primary endpoints: markers of skin barrier function and acne severity.[10]

Primarily Comedonal Acne

Comedonal acne responds most efficiently to topical retinoids which are comedolytic, anti-comedogenic, and anti-inflammatory. Many acneceuticals that are keratolytics also have anti-inflammatory activities (alpha and beta hydroxy acids, azelaic acid, retinol derivatives, and bakuchiol) and some also aid in barrier repair (alpha and beta hydroxy acids).[1] As such, keratolytic acneceuticals may accomplish or aid in the treatment of primarily comedonal acne.

Primarily Inflammatory Acne

The papules and pustules of acne are inflammatory lesions that respond particularly well to anti-inflammatory agents. Increased colonization of *C. acnes* within the pilosebaceous unit is a fundamental cause of the inflammatory process in acne. Several acneceuticals serve the dual roles of anti-inflammatory and antibacterial agents (niacinamide, bakuchiol, zinc, green tea, cannabidiol).[1]

When utilizing acneceuticals with antibacterial activity, we are seeking agents that will modify the follicular microbiome, thereby encouraging a normal, balanced diversity to regain microbiome homeostasis. Commensal *C. acnes* plays an important role in skin health, acidifying the stratum corneum by producing free fatty acids from triglycerides and reducing colonization with pathogenic bacteria. Both the quantity and quality of follicular *C. acnes* are of clinical importance in the acne-prone follicular unit. Several phylotypes of *C. acnes* exist with an overabundance of phylotype IA1 associated with more severe acne and phylotype II associated with skin health.[12,16,17] The overarching aim of therapy is to minimize IA1 rather than to eradicate the entire *C. acnes* community. There is some data demonstrating the ability to utilize isolated phylotype II *C. acnes* as a probiotic to improve skin health.[18]

Third Stratification (Figure 1 and Table 1)

The third stratification recognizes the acneceuticals most likely to accomplish the goals of therapy: sebum reduction, barrier repair, reduction of hyperkeratinization, *C. acnes* reduction, and reduced inflammation. As mentioned previously, these acneceuticals were vetted in an earlier publication as those agents with human, in vivo, single- or double-blinded, vehicle- or comparator-controlled trials.[1] Combination therapy chosen purposefully from each therapeutic goal is likely to be the most effective.

Limitations

In vetting acneceuticals for inclusion in this paper, the authors endeavored to review actives with only the highest quality data. It cannot go without noting, however, that the rigor of nonprescription studies does not mirror that of prescription products. In many cases, studies were heterogeneous in design, differed in clinical endpoints, and had small numbers of subjects. Although data utilized to create this algorithm was not limited to any race or ethnicity, the majority of the studies either did not contain patients of varied backgrounds or did not indicate race or ethnicity. As such, it is difficult to draw definitive conclusions across diverse populations or skincare products.

CONCLUSION

Acne management focuses on the use of prescription medications and procedures that aim to target the 4 pillars of acne pathophysiology. More recently, however, our understanding of the interrelationship between acne, barrier health, and microbiome diversity has led us to examine more closely the importance of nonprescription actives (acneceuticals) as monotherapy as well as adjunctive therapy. Expert opinion and consensus papers have stressed the importance of quality skin care in acne management, but this advice has yet to make its way to treatment guidelines.

Although our pharmacologic treatments are highly efficacious, clinicians continue to search for better regimens with improved safety and tolerability. Our patients search, too – with or without our guidance. Some are looking for a more "natural" approach to skin care, others for affordable options, and still others seek the satisfying sense of control that can come from successful self-prescribing. Unfortunately, the internet is replete with recommendations that fall short of effective care and may have harmful consequences.[19] Delay in acne therapy is associated with an increased risk of acne sequelae such as dyspigmentation and scarring, and uneducated postings can lead to permanent disfigurement.[20,21] It is incumbent upon clinicians to be well-versed in the use of acneceuticals - nonprescription active skin care ingredients - which alone can treat mild acne and combined with prescription medications, optimize treatment regimens. Failure to discuss skin care at every acne visit is a missed opportunity to enhance patient outcomes.

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