

# The Dermatology Provider's Role in the Antibiotic Resistance Crisis

## *An Update on Alternative Treatments for Acne Vulgaris*

Farinoosh Dadrass and Eden Lake

**ABSTRACT:** Dermatology healthcare providers commonly treat acne vulgaris with oral and topical antibiotics. In the face of the current antibiotic resistance crisis, alternative therapies should be considered prior to the use of antibiotics and antibiotics should be used sparingly. Alternative therapies include retinoid therapies, retinoid combination therapies, hormonal therapies, and light-based therapies, as well as various combinations of these therapies. Patients would benefit from the initial exclusion of an underlying endocrine pathology prior to initiating vitamin A-derived therapies, light-based therapies, or more subtle hormonal therapies.

**Key words:** Acne Vulgaris, Antibiotic Resistance, Hormonal Therapy, Light-Based Therapy, Retinoid Combination Therapy, Retinoid Therapy

Acne vulgaris is a chronic skin disease, commonly treated with oral and topical antibiotics (Del Rosso et al., 2016). This disorder affects between 40 and 50 million Americans; 85% of adolescents will experience acne at one point in their lives, and many still experience symptoms into adulthood (Canavan et al., 2016). Early intervention is necessary to preserve quality of life (Canavan et al., 2016).

Dermatologists prescribe 4.9% of antibiotic prescriptions yet only comprise 1% of the physician population (Canavan et al., 2016). Therefore, dermatology healthcare providers have a significant opportunity to combat the development of antibiotic-resistant bacteria.

The pathophysiology of acne concerns the pilosebaceous unit and is preceded by one or more of the following: colonization of the skin with the gram-positive *Cutibacterium acnes* (*C. acnes*, previously *Propionibacterium acnes*), increased levels of inflammation, elevated sebum production, and aberrant keratinization leading to both inflammatory and noninflammatory lesions (Canavan et al., 2016). Treatment of these lesions frequently involves antibiotic monotherapy (Canavan et al., 2016). Resistant strains of *C. acnes* were reported at a rate of 20%–25% in the 1970s to 1980s, which increased to a maximum of 75% by the early 2000s and decreased to 30%–40% during the 2010s (Karadag et al., 2020).

Because of the pressing nature of antibiotic resistance, alternative therapies for the treatment of acne must be utilized. There are a wide variety of alternative regimens to antibiotics, and this review will serve as an update that investigates newer agents as well as some of the more successful older agents.

### TOPICAL RETINOID THERAPIES

One regularly prescribed class of acne therapy is retinoids, including adapalene, tretinoin, and tazarotene, which are natural or synthetic derivatives of vitamin A (Jain et al., 2014). Their efficacy stems from their ability to adjust aberrant follicular keratinization (Jain et al., 2014). Retinoids are considered first-line treatment for mild-to-moderate acne, particularly comedonal acne (Jain et al., 2014). Retinoids can be used on their own or in combination therapies.

Trifarotene cream, a selective retinoic acid receptor (RAR $\gamma$ ) agonist topical retinoid, is a new promising option for the treatment of moderate acne (Tan et al., 2019). Two phase III double-blind, randomized, vehicle-controlled studies (PERFECT 1 and PERFECT 2) of trifarotene 50  $\mu$ g cream

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compared with vehicle were conducted (Tan et al., 2019). In both of these studies, trifarotene cream was proven to be the more successful treatment for moderate acne compared with vehicle cream (Tan et al., 2019). Combined with an encouraging safety profile, trifarotene cream should be considered as a favorable alternative to antibiotic treatment for acne (Tan et al., 2019).

Tretinoin lotion is another effective treatment for moderate-to-severe acne (Eichenfield et al., 2019). Two phase III multicenter, randomized, double-blind, vehicle-controlled studies found tretinoin 0.05% lotion more effective compared with vehicle (Eichenfield et al., 2019). Results showed that, by week 12, inflammatory and noninflammatory lesion counts decreased by 49.5% and 44.0%, respectively, whereas vehicle group decreased by 31.4% and 18.8%, respectively (Eichenfield et al., 2019).

### TOPICAL RETINOID COMBINATION THERAPIES

One study has shown that benzoyl peroxide (BPO) is capable of treating and eradicating antibiotic-resistant strains of *C. acnes* (Leyden et al., 2011). A study using a fixed-dose, once-daily adapalene 0.1% and BPO 2.5% combination gel on antibiotic-sensitive and antibiotic-resistant strains of *C. acnes* showed that the combination gel was significantly more effective than the respective monotherapies (Leyden et al., 2011). After applying adapalene-BPO combination gel daily, there was an 80% reduction in total *C. acnes* after two weeks and a 93% reduction after four weeks (Leyden et al., 2011). As such, retinoid combination therapy may be a successful way to directly combat the antibiotic resistance crisis.

Retinoids, both systemic and topical, can also be combined with an anti-inflammatory agent, such as topical dapson (Faghihi et al., 2014). In one randomized, double-blind study, treatment therapy for moderate-to-severe acne consisted of an oral retinoid, isotretinoin, 20 mg daily and 5% dapson gel twice daily for eight weeks compared with oral isotretinoin alone (Faghihi et al., 2014). From baseline, there was a remarkable decrease in the number of total inflammatory and noninflammatory acne lesions for the group treated with dapson (Faghihi et al., 2014). Greater efficacy was seen in women compared with men (Faghihi et al., 2014).

The combination of isotretinoin and antihistamines has been studied. Pandey and Agrawal carried out a randomized controlled trial investigating isotretinoin combined with levocetirizine in comparison with isotretinoin alone (Pandey & Agrawal, 2019). After 12 weeks of treatment of moderate-to-severe acne, there was a statistically significant decrease in the number of total inflammatory and noninflammatory acne lesions, as well as the severity of acne in the combined isotretinoin and levocetirizine group compared with isotretinoin alone (Pandey & Agrawal, 2019).

### HORMONAL THERAPIES

Hormonal therapies for acne treatment have different targets and implications in men and women, but antiandrogen therapy and opposing insulin resistance are key factors for

both. Jaisamrarn et al. conducted a study comparing safety and efficacy between two different combined oral contraceptives for treatment of mild-to-moderate acne in women (Jaisamrarn et al., 2014). The two oral contraceptives included a triphasic combination of ethinyl estradiol and norgestimate (EE/NGM) as well as the biphasic combination of ethinyl estradiol and desogestrel (EE/DSG; Jaisamrarn et al., 2014). Ethinyl estradiol decreases serum androgen levels via negative feedback on the hypothalamic-pituitary-adrenal axis, causing a reduction in ovarian testosterone production and an increase in sex-hormone-binding globulin (Jaisamrarn et al., 2014). Progestins studied in recent research, such as NGM and DSG, contribute to a reduction in androgen receptor binding (Jaisamrarn et al., 2014). Results showed a 74.4% decrease in total acne lesions with EE/NGM and a 65.1% decrease with EE/DSG (Jaisamrarn et al., 2014).

Antiandrogens, such as the off-label use of spironolactone, also treat hormonal female acne. A hybrid systematic review concluded that 200 mg of spironolactone daily decreases the number of inflamed lesion counts (Layton et al., 2017). A recent interventional longitudinal study evaluated acne in 40 female patients with a diagnosis of polycystic ovary syndrome taking metformin, an antihyperglycemic, three times daily for eight weeks (Sharma et al., 2019). The study showed a decrease in mean acne severity using a four-point Definition Severity Index assessment scale from  $80 \pm 49.29$  to  $9.703 \pm 8.5$  at the end of week eight (Sharma et al., 2019).

The same quantity of research is lacking in these therapies' effect on male acne. Another novel hormonal treatment pathway is cortexolone 17 $\alpha$ -propionate 1% cream, a potent topical antiandrogen (Trifu et al., 2011). This steroid acts by competing at the androgen receptor level without inhibiting 5 $\alpha$ -reductase in the skin (Trifu et al., 2011). Its efficacy was shown against a topical tretinoin 0.05% cream, and cortexolone 17 $\alpha$ -propionate 1% cream was found to be more effective than tretinoin or placebo in treating mild-to-moderate acne in men (Trifu et al., 2011). In addition to antiandrogens, metabolic impairments may play a role in male acne pathogenesis. Sebum production begins during puberty and corresponds to peaks in growth hormone and insulin-like growth factor 1 levels, and acne typically starts at the same time as the increase in plasma insulin (Del Prete et al., 2012). Although the relationship between a metabolic profile and acne has been shown in men, the correlation between insulin resistance and acne in men resistant to standard therapies has not been well researched (Del Prete et al., 2012).

### LIGHT-BASED THERAPIES

A third alternative is light-based therapy. This noninvasive method can be used as monotherapy or combination therapy, and its use is considered when topical or systemic treatments are contraindicated, or in resistant cases (Patidar et al., 2016). Various light sources include laser, halogen lamp,

radiofrequency, and intense pulsed light (IPL; Bakus et al., 2018; Mei et al., 2013). However, light-based therapies may not prove to be the most cost-effective solution as insurance coverage will vary.

Patidar et al. showed the effect IPL can have on acne in Indian skin by comparing normal and subnormal fluences. IPL targets *C. acnes* via selective thermal damage, causing porphyrin exposure to visible light, the achievement of an excited state, and formation of a singlet oxygen that destroys the organisms (Patidar et al., 2016). Normal fluence (35 J/cm<sup>2</sup>) was used on the right side of the face; and subnormal fluence (20 J/cm<sup>2</sup>), on the left side of the face (Patidar et al., 2016). Results showed approximately 60% reduction in acne lesions on both sides, suggesting even subnormal fluence is effective for acne treatment, while minimizing side effects (Patidar et al., 2016).

Photodynamic therapy (PDT), which uses photosensitizing agents activated by light, can also be combined with topical 5-aminolevulinic acid (ALA) and 420–950 nm of IPL (Mei et al., 2013). This addition of a photosensitizing agent leads to better results via fewer treatments and maintains longer remission (Mei et al., 2013). Compared with an IPL control group, the ALA-IPL-PDT group showed a reduction in noninflammatory and inflammatory acne lesion counts, with a mean of 83.6% and 57.5%, respectively (Mei et al., 2013). Thus, the photosensitizing agents are effective and may be particularly helpful for inflammatory acne (Mei et al., 2013).

More recently, Bakus et al. explored the use of combination long-pulsed followed by Q-switched Nd:YAG laser therapy for acne lesions (Bakus et al., 2018). Nd:YAG achieves therapeutic outcomes via the emission of infrared wavelengths that target the dermis and pilosebaceous unit (Bakus et al., 2018). After an average of 12 treatments, there was a mean reduction of 81% in acne lesions and an 80% improvement in overall skin appearance (Bakus et al., 2018). Twelve months after final treatment, a mean reduction of 86% in acne lesions and a mean improvement of 84% in overall skin appearance was observed (Bakus et al., 2018).

## CONCLUSION

There are strong alternatives available to antimicrobial therapy that, because of the impending threat of antibiotic resistance, dermatology providers should begin to consider as first-line treatments. Hormonal therapies work to correct a hormonal imbalance within individuals who do not respond to standard treatments for acne. It is imperative to diagnose these imbalances quickly, as skin disorders have a devastating psychosocial impact and scar treatment is difficult and costly. In addition, acne may be a manifestation of an underlying chronic illness yet to be diagnosed or addressed.

Among the therapies discussed in this review, each was able to show its potential role as an alternative to antibiotics for acne treatment. When aiming to avoid antibiotics for

acne therapy, retinoid, retinoid combination, hormonal, and light-based therapies are all excellent additions to a patient's regimen. Patients would benefit from first excluding endocrine pathology for severe acne and then utilizing these therapies to treat their acne while preventing future relapses. By prescribing these alternative agents, dermatology healthcare providers can effectively treat their patients' acne without further contributing to the development of harmful antibiotic-resistant bacteria. ■

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