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REVIEW ARTICLE

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Acne treatment review and future perspectives

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Abstract

Acne affects approximately 9% of people worldwide and is the most common skin condition in the USA. There are abundant topical and oral treatment options available for patients with acne. First-line agents include topical retinoids, azelaic acid, benzoyl peroxide, and combinations of these agents. For recalcitrant or more severe acne, oral medications, including oral antibiotics, isotretinoin, or hormonal therapy, may be considered. This review will also discuss the many advances being made in the treatment of acne vulgaris, from the development of microencapsulated medications to targeted treatments.

KEYWORDS
acne, acne pathogenesis, acne treatment, minocycline foam, photodynamic therapy

1 | INTRODUCTION

The global prevalence of acne vulgaris, a chronic inflammatory disease affecting the pilosebaceous unit, is estimated to be 9.38% across all ages.[1] Acne is the most common skin disease in the United States of America and over 85% of people between the ages of 12 and 25 will develop acne.[2] Although adolescents are predominantly affected, adults may also experience acne: approximately 26% of women and 12% of men in the United States of America experience acne in their 40s.[2] The prevalence of adult acne is increasing, especially in women; in fact, "adult female acne" became the terminology for acne occurring in females over the age of 25.[3] In both women and men, there are differences between the adult and adolescent forms of acne.[2] Older skin is more sensitive, presenting a therapeutic challenge as topical treatments are less tolerated.[4,5]

Acne may be inflammatory—papular or pustular acne usually attributed to *Cutibacterium acnes* (*C. acnes*)—or noninflammatory, either in the form of an open or closed comedo. Nodulocystic acne is a more severe form of acne that is characterized by nodules or cysts, and this form of acne especially has a propensity to cause scarring. *Pityrosporum* folliculitis, also known as fungal acne, is caused by infection of hair follicles with *Malassezia furfur* or other forms of *Malassezia*.[6] *Pityrosporum* folliculitis may appear clinically similar to acne vulgaris but is treated with antifungal agents and is often exacerbated if traditional acne treatments are used.[6]

Acne development may be promoted by many potential risk factors, including foods with a high glycemic index, elevated skin pH, psychological stress, comedogenic makeup and skin products, and any factor that increases androgen production, such as insulin resistance and polycystic ovarian syndrome (PCOS).[7] Reports of "maskne," a type of acne mechanica believed to be caused by occlusion of follicles and microbiome dysbiosis, emerged during the 2019 coronavirus pandemic as a result of widespread use of reusable masks.[8] While estradiol has been noted to be decreased in patients with acne, increased levels of progesterone, glucocorticoids, insulin, insulin growth factor 1 (IGF-1), and androgens have been observed in patients with acne.[7] The role of these hormones, particularly androgens, in the pathogenesis of acne has been studied extensively.

Androgens, which are known to regulate sebum production, have receptors on sebaceous glands and keratinocytes.[9] Hyperkeratinization may lead to the formation of a keratin plug at the follicular infundibulum, and increased amounts of sebum and keratin may also lead to progression of a microcomedo into a closed comedo (commonly referred to as "whiteheads"). Closed comedones and open comedones (commonly referred to as "blackheads") are the two main lesions of non-inflammatory acne. Increased sebum production, *C. acnes*, inflammation, and follicular hyperkeratinization are the major factors involved in the pathogenesis of acne.[2]

C. acnes is believed to propagate acne pathogenesis through several mechanisms, including driving the inflammatory response and

allowing for follicular hyperkeratinization.[9] Sebum is thought to facilitate *C. acnes* growth, and this bacteria has been shown to alter the lipid composition of sebum to increase pro-inflammatory free fatty acids, which lead to the production of inflammatory cytokines.[9] Certain cytokines, such as interleukin (IL)-1, are believed to be necessary for comedo formation and are secreted by keratinocytes due to activation by *C. acnes*.[9] IL-1 has been shown to increase keratinocyte proliferation and lead to autocrine production of IL-1, thus further promoting the development of comedones.[9] Acne may be induced by dysbiosis of the skin barrier through the imbalance of different *C. acnes* phylotypes including phylotype IA1, which has been shown to be highly associated with acne.[10] Changes to the skin microbiome may foster an environment that allows for the proliferation of *P. acnes*. The gut microbiome may also be involved with acne by interacting with the skin microbiome through systemic release of inflammatory mediators.[11,12]

An additional cause of skin barrier dysfunction resulting in bacteria proliferation and subsequent comedo formation includes stratum corneum pH levels. In some studies, patients with acne were found to have higher facial skin pH than those without acne.[13] The pathophysiology involves increased skin pH inducing stratum corneum instability and allowing microorganisms to proliferate and produce inflammatory cytokines.[13,14]

The four main factors—sebum production, *C. acnes*, inflammation, and hyperkeratinization—that contribute to the pathogenesis of acne may each be targeted with different oral and topical medication.

2 | ACNE TREATMENTS

Acne is one of the most common skin conditions that dermatologists treat. There is a myriad of oral and topical treatment options for acne, as well as several novel treatment modalities in development that will be discussed.

2.1 | Topical medications

2.1.1 | Antibacterial agents

Three topical antibiotics are approved by the United States of America Food and Drug Administration (FDA) to treat acne: clindamycin, erythromycin, minocycline, sodium sulfacetamide, and sulfur. Topical antibiotics are considered first-line treatment for acne, and clinical response may take up to 12 weeks to be observed. Even after this amount of time, complete resolution of acne is not guaranteed.

Topical clindamycin is available alone in various concentrations and forms including lotions, foams, and gels (e.g., Clindagel); however, due to antibiotic resistance, monotherapy is not recommended.[15] As such, topical clindamycin may be combined with benzoyl peroxide (BenzaClin and DUAC®) and with tretinoin (Veltin). Although generally well-tolerated, medications containing topical clindamycin may cause dry or irritated skin.

Topical erythromycin may be used as an alternative to topical clindamycin; however, the latter is generally preferred due to concern for higher rates of *C. acnes* resistance to topical erythromycin.[15] Due to these concerns, topical erythromycin should be used in combination with other agents, such as benzoyl peroxide (Benzamycin®), although topical erythromycin is available as monotherapy in the form of 2% gels, swabs, or solutions. Topical erythromycin is generally well tolerated but may cause skin irritation.

Topical dapsone, available as a 5% or 7.5% gel, may be used in patients with inflammatory papulopustular acne who fail initial therapy.[2,15] As this medication appeared to have more benefits for adult, female patients in clinical trials, topical dapsone may be used as first-line therapy for females, especially those with darker skin tones, with acne, and in patients with sensitive skin.[2] The mechanism of this drug is not well understood. This agent may cause skin irritation, although side effects are often minimal, and unlike oral dapsone, patients using topical dapsone do not need to undergo glucose-6-phosphate dehydrogenase testing.[16] Importantly, topical dapsone should not be used in conjunction with benzoyl peroxide, as this combination can cause skin discoloration.[2]

Topical minocycline, a tetracycline derivative, may be used as an alternative to topical antibiotics. Three phase 3 trials found topical minocycline 4% foam to be more effective than foam vehicle.[17,18] Amzeeq™, 4% minocycline topical foam, was approved in 2019 by the FDA to treat moderate-to-severe, non-nodular acne in patients older than age 9. This drug is lipophilic and moves through sebum to the pilosebaceous unit.[19] Although the exact mechanism of this drug is not well understood, studies have shown that this agent possesses potent antibacterial effects.[19] Many studies showed that topical minocycline 4% foam was effective at improving acne within 12 weeks; however, a 40 week extension study showed that patients taking this drug continued to show improvement at 52 weeks after treatment.[19,20] Most patients enrolled in clinical trials studying topical minocycline 4% foam tolerated this drug well, with increased creatinine phosphokinase levels and headaches reported as the most common adverse events.[17,18]

Topical sodium sulfacetamide is a bacteriostatic antibacterial that functions by halting bacterial DNA synthesis through inhibiting para-aminobenzoic acid. It is usually used to treat acne as a lotion consisting of 10% sodium sulfacetamide and 5% sulfur. Studies have shown reduction in acne lesions of 50% to 69% after 8 weeks and 78% after 12 weeks.[21,22] Sulfur and sodium sulfacetamide have side effects that are well tolerated and seldomly occur, including skin dryness, skin astringence, and itching.[22–24]

While 1% to 10% topical sulfur can be used to treat mild-to-moderate acne on its own due to its keratolytic, antifungal, and bacteriostatic properties,[24] the therapeutic effect is improved when used with sodium sulfacetamide or benzoyl peroxide.[22,23,25–27] Sulfur interacts with cysteine in keratinocyte to produce hydrogen sulfide that can rupture disulfide bonds, causing a keratolytic effect.[28] Recently, sulfur nanoparticle preparations have demonstrated effectiveness against *Staphylococcus* bacteria.[29] *Staphylococcus* bacteria can affect acne pathogenesis by introducing drug resistance virulence factors.[30]

2.1.2 | Benzoyl peroxide

Benzoyl peroxide—available as part of a gel, cream, or wash that may be left on the skin or washed off—is one of the major first-line antimicrobial agents used to treat mild-to-moderate acne via its antimicrobial, anti-inflammatory, and keratolytic properties.[31] After benzoyl peroxide is broken down into benzoic acid and hydrogen peroxide, this drug reduces *C. acnes* concentration through the generation of free oxygen radicals; thus, the use of benzoyl peroxide does not allow for microbial resistance.[2] This drug is generally applied once per day and improvement in acne may occur as soon as 5 days, but are expected 3 weeks after starting benzoyl peroxide, with the maximum lesion reduction apparent after 8 to 12 weeks of use.[16] Studies have shown that 2.5%, 5%, and 10% formulations of this medication have a similar time required for clinical response and are equally effective; however, higher concentrations may cause irritant dermatitis.[31] Other adverse effects include xerosis, scaling, erythema, hypersensitivity, and contact sensitization reactions.[16] Benzoyl peroxide can also increase transepidermal water loss, altering skin barrier function.[32] Because the continued use of this drug is required to maintain its effects, side effects have been noted to resolve with decreased use or lower concentrations.[16] Patients should be advised that benzoyl peroxide may stain or bleach fabric. Combining benzoyl peroxide with other agents, such as topical retinoids or antibiotics, has been shown to enhance its efficacy in treating acne.[31] Benzamycin, for example, combines 3% erythromycin with 5% benzoyl peroxide in the form of a topical gel and has been shown to be more effective and equally as tolerable as benzoyl peroxide monotherapy.[33]

2.1.3 | Azelaic acid

Possessing comedolytic, antimicrobial, and mildly anti-inflammatory properties, Azelaic acid is available in the form of a 15% gel and a 20% cream: Finacea and Azelex, respectively. These agents may be used twice daily as first-line therapy for mild-to-moderate inflammatory and non-inflammatory acne.[34] Azelaic acid is especially beneficial in those with sensitive skin or in individuals with dyspigmentation, as this agent has lightening effects.[34] In addition to hypopigmentation, side effects may also include skin irritation, although side effects are minimal.[2] This drug is category B in pregnancy, and may also be used in females who are lactating. When combined with other agents, such as topical antibiotics, azelaic acid may have enhanced efficacy.[34]

2.1.4 | Topical retinol and retinol derivatives

When administered either as in combination formulations or monotherapy, topical retinoids serve as first-line treatment for acne vulgaris (Tables 1 and 2).[35] Retinol is a vitamin A derivative that works to decrease keratinocyte proliferation and differentiation via transcription alteration—these molecules bind to retinoid X and retinoic acid

TABLE 1 First-line therapies for adolescents and young adults[16]

Acne severity	Medication type		
Mild	Benzoyl peroxide	Topical retinoid	Topical combination therapy: Benzoyl peroxide + antibiotic; or Retinoid + benzoyl peroxide; or Retinoid + benzoyl peroxide + antibiotic
Moderate	Topical combination therapy: Benzoyl peroxide + antibiotic; or Retinoid + benzoyl peroxide; or Retinoid + benzoyl peroxide + antibiotic	Oral antibiotic + topical retinoid + benzoyl peroxide	Oral antibiotic + topical retinoid + benzoyl peroxide + topical antibiotic
Severe	Oral antibiotic + topical combination therapy: Benzoyl peroxide + antibiotic; or Retinoid + benzoyl peroxide; or Retinoid + benzoyl peroxide + antibiotic	Oral isotretinoin	

TABLE 2 Alternative therapies for adolescents and young adults[16]

Acne severity	Medication type			
Mild	If not on already, add topical retinoid or benzoyl peroxide	Can consider alternate retinoid	Can consider topical dapsone	
Moderate	Can consider alternate combination therapy	Can consider changing oral antibiotic	If female, may add oral spironolactone or combined oral contraceptive	Can consider oral isotretinoin
Severe	Can consider changing oral antibiotic	If female, may add oral spironolactone or combined oral contraceptive		Can consider oral isotretinoin

receptors within a keratinocyte's cytoplasm, subsequently translocating to the keratinocyte nucleus and inducing changes in transcription. Rentinoids may also alter the skin barrier function by increasing transepidermal water loss, so efforts to minimize this side effect should be made.[32] Retinoids may also affect skin microbes by blocking nutrient supply and stabilizing the hyperreactivity of the immune system.[36] Currently, there are four FDA-approved generations of topical retinoids: tretinoin, also referred to as all-trans retinoic acid (ATRA, first generation); adapalene and tazarotene (third generation); and trifarotene (fourth generation).

Trifarotene (AKLIEF®) has greater selectivity than the other generations of retinoids, binding specifically to the retinoic acid receptor gamma, which is predominantly present in the epidermis.[37] Because of its hepatic instability, it is safer than other retinoids.[36] In two double-blind, randomized, vehicle-controlled studies, trifarotene 50 μg/g cream demonstrated significant decreases in the number of non-inflammatory (49.7% vs. 35.7% in the first study and 57.7% vs. 43.9% in the second study [$p < 0.001$]) and inflammatory (54.4% vs. 44.8% in the first study and 66.2% vs. 51.2% in the second study [$p < 0.001$]) lesions in 12 weeks compared to the vehicle.[38] A longer, 52-week study confirmed that trifarotene was successful at treating acne at a rate of 57.9% based on investigator global assessment and physician's global assessment rating of no or almost no acne.[39] The most common side effects reported included mild itching, irritation, and sunburn to the treated areas.[40] Despite trifarotene's demonstrated success as an acne treatment, its high cost may be prohibitive to many patients.[40]

Recently, tretinoin and benzoyl peroxide have been combined into one medication. Historically, tretinoin and benzoyl peroxide were not produced as combination products as the tretinoin molecule is unstable—it is easily oxidized, isomerizes upon exposure to radiation, and thermally unstable.[41] However, one study has shown that an optimized formulation of tretinoin gel (0.05%) and benzoyl peroxide resulted in zero degradation of tretinoin after 7 h.[41] Another study evaluated the efficacy of benzoyl peroxide and microencapsulated tretinoin gel, either used in combination or sequentially.

Microencapsulated benzoyl peroxide 3% and tretinoin 0.1% (Twyneo®) was FDA-approved in July of 2021 using Sol–Gel's patented technology and is the first fixed-dose combination topical medication in the treatment of acne vulgaris. The most common adverse effects associated with topical retinoid use are drying, stinging, and burning upon application.[42] Tretinoin 0.05% (Altreno®) is formulated with marine collagen derived from sole fish, sodium hyaluronate, and glycerin as humectants to alleviate the associated dryness that typically occurs with topical retinoids; only 1% of patients reported experiencing skin irritation in clinical trials. However, it must be used cautiously in patients with fish allergies or sensitivities as the collagen in this formulation is derived from sole fish.[43]

2.1.5 | Salicylic acid

Salicylic acid, a comedolytic and mildly anti-inflammatory agent, can be used in patients with mild acne who cannot tolerate topical retinoids or benzoyl peroxide, although there are few clinical trials supporting its efficacy. This agent is available in several wash-off and leave-on forms and is available at concentrations of 0.5% to 2% over the counter.[16] Salicylic acid may be used in conjunction with benzoyl peroxide, and higher concentrations of salicylic acid may be used to perform superficial chemical peels.[2]

2.1.6 | Clascoterone

Clascoterone (Winlevi, cortexolone 17 α-propionate) 1% cream is the first FDA-approved medication with a novel mechanism of action since the introduction of isotretinoin (Accutane) in 1982, according to the manufacturers of Clascoterone. This medication competes with dihydrotestosterone (DHT) for androgen receptor binding on the skin, thereby decreasing androgen-responsive gene transcription. This decrease in transcription results in less sebum and pro-inflammatory cytokine production.[44,45] Clascoterone offers anti-inflammatory and anti-androgenic effects without the potential of systemic adverse effects, which may occur if acne vulgaris is treated with systemic hormonal medications such as COCs and oral spironolactone.[46,47] Akin to Amzeeq®, clascoterone's role in the acne vulgaris treatment algorithm is unknown but provides dermatologists with another choice of treatment if other modalities fail.

2.2 | Oral medications

2.2.1 | Antibacterial agents

Oral antibiotics may be considered for patients with moderate-to-severe acne or patients with inflammatory acne resistant to topical medications.[16] Many classes of oral antibiotics may be used in the treatment of acne, including penicillins (amoxicillin and ampicillin), macrolides (azithromycin and erythromycin), tetracyclines (doxycycline, minocycline, and sarecycline), and several others. These medications improve acne by decreasing the concentration of *C. acnes*. Potential side effects of oral antibiotics are numerous and widely vary between classes; however, one adverse effect that is consistently reported across most antibiotic classes is gastrointestinal upset. In addition to reducing levels of *C. acnes*, oral antibiotics may interfere with the normal gut flora, thus causing gastrointestinal symptoms. Oral antibiotics may be given in conjunction with topical retinoids and benzoyl peroxide, and once clinical improvement is achieved, effects may be maintained with topical medications after oral antibiotics are discontinued.[2]

Tetracyclines, which inhibit the 30S subunit of bacterial ribosomes, are the first-line antibiotic treatment for non-pregnant patients over the age of 8 who have moderate-to-severe acne.[16] Sarecycline, a second-generation tetracycline approved by FDA in 2018, may cause fewer side effects than other tetracyclines because it is a narrow-spectrum agent that may cause fewer alterations in the gut microbiome.[48] Special attention must be given to patients under the age of

8 and patients who are pregnant or breastfeeding, as certain antibiotics are contraindicated.

There is debate on whether topical and oral antibiotics should be used for acne due to concerns of growing antibiotic resistance.[46] To mitigate this risk, alternatives should be considered, including benzoyl peroxide with a topical retinoid instead of topical antibiotics. When necessary for moderate to severe acne, oral antibiotics should be combined with a topical retinoid or benzoyl peroxide, or their combination.[46] Limiting the duration of use to no more than 3 months is advised.

2.2.2 | Oral retinoids

Isotretinoin, an oral synthetic vitamin A analog, may be considered in non-pregnant patients 12 years of age and older with moderate-to-severe acne who have failed other treatments, including oral antibiotics, or patients who have recalcitrant nodulocystic acne.[2] This medication may also be used in patients with less severe acne if they have significant scarring.[2] Oral isotretinoin has been documented to have some of the best treatment adherence rates and satisfaction rates compared to topical therapies and oral antibiotics.[49,50] Generally administered as monotherapy for several months, isotretinoin is the only treatment for acne that targets all four pathogenic mechanisms of acne (sebum production, *C. acnes*, inflammation, and hyperkeratinization). Although Accutane™ is no longer available in the United States of America, Isotretinoin is still available in generic forms (e.g., Amnesteem and Claravis).[51] One appealing feature of isotretinoin is that it may induce remission of acne after a minimum cumulative dose of 120 mg/kg. Some studies have shown that maintaining treatment for 2 months after acne completely resolves decreases the risk of acne relapse.[52]

Side effects may include mucocutaneous dryness, myalgias, elevated aminotransferase, and hyperlipidemia.[51] Current guidelines recommend monitoring transaminases and the patient's lipid profile at baseline and at regular intervals until levels stabilize.[53] Even if levels are elevated, these effects appear to be short-lived and reversible, and do not necessarily warrant discontinuation.[54] Several serious side effects have been reported with isotretinoin, including increased incidence of mood changes, such as depression and suicidality, and inflammatory bowel disease.[51] However, robust evidence linking isotretinoin use to these conditions is lacking. Isotretinoin is a known teratogen, and in the United States of America, the FDA regulates the use of this medication through the iPLEDGE program to minimize the risk of fetal exposure.[55] Providers and pharmacies must be enrolled in this program to prescribe isotretinoin, and patients with childbearing potential must use two specific forms of contraception and comply with monthly pregnancy tests.[55]

Absorica LD™, another oral retinoid, was approved by the FDA in 2019 to treat nodular acne. Unlike other oral retinoids, Absorica LD™ uses micronized technology to decrease the size of isotretinoin, enabling more efficient intestinal absorption.[56] Because of this, isotretinoin can be prescribed at lower doses and without food, potentially reducing the undesirable side effects and challenging diet constraints patients taking isotretinoin have faced in the past. Absorica LD™ 32 mg was determined to have the same bioavailability as isotretinoin-lidose 40 mg with food and double the bioavailability without food.[56]

2.2.3 | Hormonal medications

Though many hormones—androgens, estrogens, insulin, insulin-like growth factor, and several others—have been implicated in acne pathogenesis, androgens are the major culprit. Androgens, like testosterone and DHT, increase sebum production and often cause nodulocystic, sudden-onset acne that may be resistant to conventional treatments.[57] As androgens produced by the ovaries contribute to acne development, female patients have the option of taking oral contraceptives with or without spironolactone to treat inflammatory, hormonal acne.

Combined oral contraceptives (COCs) contain both estrogen and progestins, which lead to decreased action of androgens through several mechanisms, including decreased sebum production.[57] Four COCs have been approved by the FDA for treatment of moderate acne in females: Beyaz (drospirenone/ethinyl estradiol/levomefolate), Estrostep Fe (norethindrone acetate and ethinyl estradiol), Ortho Tri-Cyclen (norgestimate and ethinyl estradiol), and Yaz (drospirenone and ethinyl estradiol). Clinical improvement may take up to 6 months to be observed, and after 6 months of use, COCs are as effective as oral antibiotics.[2]

COCs are first-line in the treatment of female patients with PCOS.[57] Side effects include breast tenderness, mood changes, gastrointestinal symptoms (e.g., nausea and vomiting), weight gain, headache, and breakthrough bleeding.[58] Because COCs can increase the risk for thromboembolism, the use of COCs is contraindicated in patients who are at an increased risk for thromboembolic disease, including those with a history of thromboembolism or migraine, and in patients 35 years or older who smoke.[16] Additionally, the use of COCs is not recommended in patients until 1 year after menstruation onset due to concerns about bone density.[58]

Spironolactone is a potassium-sparing diuretic that antagonizes androgen receptors, thus decreasing free testosterone levels and the size and activity of sebaceous glands.[57] Although traditionally prescribed for hormonal acne in female patients, spironolactone has been shown to be effective in all types of acne and may also be used in male patients.[59] This medication is generally well-tolerated, although previously, electrolytes were monitored due to concern for hyperkalemia. Recent studies, however, have found that serum potassium monitoring is unnecessary due to inadequate evidence that young, healthy patients taking this medication develop hyperkalemia.[60] For patients with recalcitrant hormonal acne that fails conventional treatment, endocrine evaluation should be considered to rule out medical conditions, such as those causing hyperinsulinemia, hyperandrogenism, or virilization.[57]

2.3 | Other treatment options

Although large studies are lacking, smaller studies indicate that phototherapy, chemical peels, drainage, and extraction, and steroid injections may improve acne and decrease scarring associated with acne. Light therapy, which is generally clinician-administered, has been shown to be as effective or more effective than traditional therapies for mild-to-moderate inflammatory acne in several small studies.[61–63] Ideal treatment parameters have not yet been established.

Superficial chemical peels using glycolic acid or salicylic acid may be used in patients with comedonal acne, although multiple treatments are necessary and the effects are generally temporary.[64] A split-face randomized trial comparing glycolic acid and salicylic acid peels in 20 participants showed that both drugs had similar efficacy in reducing lesions after 12 weeks of treatment.[65] However, only areas treated with salicylic acid continued to have decreased acne lesions 8 weeks after treatment was discontinued.[65] Chemical peels may cause dyspigmentation in individuals with Fitzpatrick skin types IV and higher, and cause significant irritation in individuals taking oral retinoids.[64]

In individuals with resistant comedones, comedo extraction can be considered in addition to using topical therapies; however, scarring may occur with this procedure.[16] For patients with nodular or cystic acne, intralesional glucocorticoid may be considered if the lesions are large.[16] Although patients will experience rapid improvement, this treatment may also cause local atrophy if used too often or if used at high concentrations.[16]

Other treatment options have been emerging in the field including cannabidiol, probiotics, and anti-microbial peptides. Studies have shown cannabidiol, the non-psychoactive biochemical component of *Cannabis Sativa*, inhibits lipogenesis in sebocytes and decreases inflammation and proliferation of these cells without significant side effects.[66] Oral probiotics are a potential adjuvant therapy for mild-to-moderate acne.[67] Probiotics were shown to decrease the amount of *P. acnes* on the skin and suppress inflammation by inhibiting IL-8.[67,68] Antimicrobial peptides (AMPs) bind to pathogens and activate the immune response, providing the initial immune defense in multicellular organisms.[69] Topical application of 5 mg/ml of engineered analogs of these AMPs, known as designed antimicrobial peptides, have shown limited toxicity while selectively inhibiting and killing antibiotic resistant strains of *C. acnes*.[69] This treatment may be important in addressing increased rates of antibiotic resistance in acne vulgaris.

2.4 | Future directions

Multiple advances are being made in the treatment of acne vulgaris, from the development of microencapsulated medications to targeted treatments. Notably, future therapies should aim to increase compliance, as adherence to current treatments is often impeded by the side effects of skin irritation, photosensitivity, antibiotic resistance, and regimen complexity.[70] Topical formulations that incorporate more than one medication into a single preparation, such as the recently approved benzoyl peroxide 3% and tretinoin 0.1% (Twyneo®), may allow for better treatment adherence, as the application of one topical formulation is simpler than the application of multiple.[71,72] A six-arm, randomized, double-blind, placebo-controlled Phase 2 clinical trial of 726 subjects determined that the combination of benzoyl peroxide and tretinoin resulted in a significant decrease of inflammatory and non-inflammatory acne lesions compared to a vehicle ($p < 0.001$).[73] Additionally, the combination led to more favorable efficacy compared to its active components alone. The mechanism for combination therapies resulting in greater efficacy may be due to the compounded effect of targeting multiple pathways as well as a potential synergistic effect such as from decreasing the development of antibiotic-resistant strains of *P. acnes*.[74,75] Other combinations of topical therapies such as benzoyl peroxide and erythromycin, benzoyl peroxide and clindamycin, and clindamycin and tretinoin have similarly demonstrated significant improvements in inflammation, the number of inflammatory lesions, and *P. acne* proliferation.[75]

A multicenter, randomized, double-blind, 12 week, phase 3 study evaluated the efficacy of a fixed-dose clindamycin phosphate 1.2%, benzoyl peroxide 3.1%, and adapalene 0.15% gel (IDP-126 gel, NCT04214639).[76] This formulation is the first triple-combination drug to be developed and tested in the treatment of acne vulgaris and shows promising results. Participants were randomized to receive either IDP-126 ($n = 147$), vehicle gel ($n = 148$), or one of the three component dyads (benzoyl peroxide/adapalene ($n = 150$), clindamycin/benzoyl peroxide ($n = 146$), or clindamycin/adapalene ($n = 150$)) once daily for 12 weeks.[76] Participants randomized to the IDP-126 cohort had significantly greater absolute mean reductions in inflammatory and noninflammatory lesions from baseline to week 12 as compared to the other cohorts.[76] Also, 52.5% of the participants in the IDP-126 cohort attained treatment success at week 12, which is significantly greater than the vehicle gel cohort (8.1%, $p < 0.001$) and the three dyad gels (range 27.8%–30.5%; $p \leq 0.001$).[76]

Despite promising research results on new therapeutic combinations, the cost-effectiveness of such treatments needs to be carefully considered by the clinician and weighed against the potential benefits. Prices of these prescription drugs are high and are often not covered by insurance.[77]

Both Twyneo® and IDP-126 utilize micronization of one or more of their components, both benzoyl peroxide and tretinoin in Twyneo® and benzoyl peroxide and adapalene in IDP-126. The microencapsulation of these ingredients allows for better penetration of the pilosebaceous units as well as potentially inhibiting the degradation of more sensitive ingredients, such as tretinoin.[78] Topical 4% minocycline foam (Amzeeq®, FMX-101) is another medication that uses micronization to its advantage. Akin to retinoids, minocycline is also prone to oxidation and epimerization, especially when exposed to moisture and light.[79] To combat minocycline's instability, it was micronized into minocycline hydrochloride crystals and suspended in a foam base.[79] Amzeeq® was the subject of multiple 12 week, phase III clinical trials as well as an open-label extension study utilizing a cohort from two of the 12 week, phase III trials.[18,20] Approved by the FDA in 2019 for moderate-to-severe acne vulgaris in patients 9 years of age and older,

Amzeeq® has a relatively safe side effect profile with the most common adverse effects from clinical trials being mild erythema, mild inflammatory/post-inflammatory hyperpigmentation, and mild dryness. Currently, the role of Amzeeq® in the milieu of available medications is unknown but offers dermatologists another option for topical antibiotic therapy.

Another strategy that is being considered in the treatment of acne vulgaris is the application of immunotherapy via biological antibodies. As we better understand the pathophysiology behind the development of this disease, it has been elucidated that *C. acnes* stimulates sebocytes, Langerhans cells, and infundibular keratinocytes via toll-like receptor 2 (TLR-2) to produce IL-6, IL-8, and IL-12, tumor necrosis factor-alpha (TNF-α), and interferon-gamma (IFN-γ).[80] Acne lesions have been shown to express IL-17, IL-23, and TNF-α and *C. acnes* also may also stimulate the production of TNF-α, IL-8, IL-1β, and matrix metalloproteinases.[81] Also, IGF-1 may promote sebocyte proliferation and differentiation.[80] These molecules may serve as targets for the treatment of acne vulgaris.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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