Solodyn and Updates on Topical and Oral Therapies for Acne

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Abstract Acne vulgaris is a chronic and ubiquitous skin condition that can result in both physical and psychological scarring. The need for early and aggressive treatment of acne is essential to prevent these deleterious effects. Understanding of acne pathophysiology continues to evolve, leading to new therapeutic targets and the development of advanced treatment regimens. Among the most recent advances in acne therapy are new fixed-drug combination therapies and novel vehicle technologies. Additionally, as the concern for antibiotic resistance grows, treatments involving nonantibiotic therapies are growing in popularity. Dermatologists have also begun to recognize the importance of diet effects on acne progression, as well as the therapeutic role of procedural acne treatments. This review summarizes the most recent developments in acne pathophysiology and discusses new trends in therapy.

Keywords Dermatology · Dermapharmacology · Therapeutic development · Acne · Pathophysiology · Treatment guidelines · Topical acne treatment · Combination topical therapy · Innovative drug delivery systems · Formulation · Antibiotics · Antibiotic resistance · Diet · Light · Laser · Photopneumatic therapy · Retinoid · Nanoparticles · Microspheres

Introduction

Acne vulgaris is one of the most common cutaneous disorders, affecting more than 80 % of adolescents and frequently persisting into adulthood [1]. Acne is a chronic condition of the pilosebaceous unit (PSU), which is characterized by inflammatory lesions (papules, pustules, and nodules) and noninflammatory lesions (open and closed comedones). In 2009, the Global Alliance to Improve Outcomes in Acne published an update on the management of acne vulgaris, emphasizing the importance of viewing acne as a chronic disease [2•]. Because of its chronicity, acne is treated over prolonged periods of time, and patients often suffer from long-term physical and psychological effects. Thus, the expert panel comprising the Alliance encouraged early and aggressive acne treatment.

This review begins with a discussion of the most recent updates in acne pathophysiology. The latest advances in acne therapy—including new fixed-drug combinations, advanced treatment formulations, and novel medications—are subsequently addressed. Finally, insights into the influence of diet on acne and the efficacy of procedural treatments for acne are offered.

Pathophysiology of Acne: The Old and The New

The pathogenesis of acne is multifactorial and has been attributed to four primary pathogenic factors: excess sebum production, follicular colonization by *Propionibacterium acnes* (*P. acnes*), alteration in keratinization, and inflammation [3]. Traditionally, the microcomedo was believed to be the primary lesion in acne, which later developed into an inflammatory or noninflammatory lesion. The formation of comedones was believed to result from failure of

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keratinocytes to separate from one another [4•]. The formation of the keratin plug and increased sebum production was then thought to be followed by colonization with *P. acnes*, and ultimately induction of the innate immune response leading to inflammation. *P. acnes* appears to activate the inflammatory cascade through Toll-like receptors (TLRs), specifically TLR-2 [5]. However, recent evidence has called this traditionally accepted sequence of events into question. This evidence suggests that inflammation may precede these other events. Jeremy et al. [6] suggest inflammation may precede keratinization and noted the presence of elevated levels of proinflammatory cytokine interleukin (IL)-1, even prior to follicular plugging. Additionally, new data suggests that the secretion of a biofilm by *P. acnes* may act as an “adhesive glue,” facilitating comedogenesis [7]. Treatment targeting the *P. acnes* biofilm is likely the target of photopneumatic therapy, a procedural technique used in acne treatment (see “Photopneumatic Therapy”).

New insights into the mechanism of activation of the androgen receptor and subsequent sebum production have also been proposed. It has long been known that androgenic hormones stimulate androgen receptors, ultimately leading to increased sebum production. Melnik [8, 9•, 10, 11] postulates that the removal of the polypeptide nuclear transcription factor FoxO1 “opens” the androgen receptor so that it can be accessed by androgenic agonists. It is the phosphorylation of FoxO1 that facilitates its removal from the androgen receptor. It is thought that increased levels of IGF-1 and insulin mediate this phosphorylation [8, 9•, 10, 11]. Certain dairy products and high-glycemic load diets are thought to play a role in enhancing this mechanism.

New data suggests that the sebaceous gland is regulated by neuropeptides and can serve as an independent neuroendocrine organ [12•]. The corticotrophin-releasing hormone (CRH) is activated by proinflammatory cytokines in response to stress [13]. CRH and CRH receptor (CRH-R) were found in SZ95 sebocytes in vitro and human sebaceous glands in situ [14, 15], suggesting a link between CRH, stress, and acne. A CRH-R antagonist known as alpha-helical CRF was found to block the effects of CRH on the SZ95 sebocyte, thereby elucidating a role for the development of CRH antagonists in the treatment of acne [16]. Moreover, melanocortins and their receptors have been identified in human skin and may prove to be clinically useful for the treatment of excessive sebum production in acne [12•, 17–19]. The response of skin to stress and its relationship to neuroendocrine function may soon present new targets for therapeutic interventions.

Current Treatment Guidelines

The Global Alliance to Improve Outcomes in Acne created recommendations for acne treatment in 2003 [20] and

published an update in 2009 [2•]. Acne treatment is based on the graded severity of acne lesions from mild to moderate to severe acne. The Alliance supports the use of fixed-dose topical combination products, as they increase efficacy by targeting multiple pathogenic factors and promote increased patient adherence. The report suggests using topical retinoids in all patients with acne except those with the most severe cases. When inflammatory lesions are present, a topical retinoid should be used in combination with an antimicrobial agent such as benzoyl peroxide (BPO) or an antibiotic. Based on published data, the Alliance suggests the limitation of oral antibiotic therapy to a period of less than 3–4 months and maintenance therapy using a topical retinoid or a topical retinoid-antibacterial combination.

The Alliance also recognizes the role of antibiotic resistance in acne management. It acknowledges the need to limit both the frequency and duration of antibiotic use. When long-term antibiotic use is necessary, the Alliance recommends adding a nonantibiotic antimicrobial agent like BPO. Unlike antibiotics, BPO has not been associated with bacterial resistance.

The 2009 update presents an in-depth discussion of the role of procedural treatments in acne [2•]. The report addresses the potential benefit of these techniques but emphasizes the need for randomized controlled trials (RCTs) to further investigate the efficacy and short- and long-term effects of treatment.

Advances in Topical Acne Treatment

Topical therapies are the mainstay of treatment for mild to moderate acne and are used as maintenance therapy for all levels of acne. Retinoids (adapalene, tazarotene, tretinoin) and retinoid-like medications (salicylic acid) have comedolytic effects, and act to reverse abnormal desquamation [21]. Retinoids have also been shown to modulate the inflammatory response associated with acne [22]. Topical antibiotics and BPO are antibacterial agents that inhibit the proliferation of *P. acnes* [23–25]. Acne treatment often requires the use of several of these medications to address the multifactorial nature of the disorder [2•, 20]. Although effective, topical medications are associated with several side effects—including dryness, irritation, and scaling—that compromise patient compliance and ultimately decrease therapeutic efficacy. New combinations and formulations of topical treatments have been developed to contend with these concerns.

Combination Topical Therapy

Dermatologists and researchers are continuously investigating optimal drug combinations in the treatment of acne vulgaris. A PubMed search for RCTs of topical combination

acne medications using the keywords *topical acne treatment*, *acne therapy*, *combination acne treatment*, and *topical combination acne* was performed for the period of December 2010 to December 2011 (Table 1).

Fixed-dose combinations of acne treatment represent the new direction for acne therapy, as they promote patient adherence and subsequently improve efficacy. The most recent RCTs involving fixed-dose combination therapy are marked by an “*” in Table 1. Studies have demonstrated that simplifying treatment regimens could lead to improved adherence and outcomes with topical acne medication [26•]. Twenty-six patients with mild to moderate acne were randomized to receive a fixed-dose combination clindamycin phosphate 1.2 %-tretinoin 0.025 % gel (CTG) known as Ziana® (Medicis, Scottsdale, Arizona), or a generic clindamycin phosphate gel 1 % (C gel) and a separate tretinoin cream 0.025 % (T cream) to apply to the entire face. Adherence to treatment was monitored with the Medication Event Monitoring System® (AARDEX Group, Sion, Switzerland), which monitors when the medication was opened. A statistically significant difference in adherence between groups was noticed at 12 weeks ($P<0.02$) with the CTG group demonstrating greater adherence. Both groups had significant improvement in inflammatory and total lesion counts ($P<0.05$) by 12 weeks. However, the CTG group showed a trend toward greater improvement from baseline than the C gel +T cream group at each time point in the study, even though statistical significance was not reached. The authors suggest the lack of statistical significance may be a result of the small sample size and the likelihood that patients will reduce the use of treatments as their condition improves [26•]. Another combination therapy that has improved medication compliance in the treatment of acne is adapalene 0.1 % and BPO 2.5 % (Epiduo®, Galderma, Fort Worth, Texas), which is further discussed in the section “*Microspheres*.”

Innovative Drug Delivery Systems

New drug delivery systems for topical medications have moved to the forefront of acne research. Drug delivery systems such as liposomes, microspheres, and solid lipid nanoparticles (SLNs) enhance follicular targeting to allow high concentrations of the active drug to penetrate the PSU [27–29]. Additionally, these systems allow for controlled release and gradual distribution of therapy, leading to reduced irritancy and side effects.

Liposomes

Liposomes are among the first generation of the novel drug delivery systems. They are spherical vesicles formed of one or more concentric phospholipid bilayers containing a central aqueous cavity [30•]. The biphasic nature of liposomes allows for carriage of hydrophobic and lipophilic medications. The

use of drug-loaded liposomes for the treatment of acne has been widely reported [30•]. A recent double-blind clinical trial compared the safety and efficacy of liposome-encapsulated 1 % clindamycin lotion to 1 % clindamycin solution [31]. At the end of 6 weeks, patients treated with the liposome-encapsulated 1 % clindamycin lotion showed a 33.3 % decrease in open comedones versus only a 8.3 % decrease in the commercial clindamycin lotion. Reports have also indicated the effectiveness of liposomal derivatives of tea tree oil, salicylic acid, retinoids, and BPO in acne treatment [30•].

Microspheres

Microsphere is a vehicle technology comprised of inert particles made of synthetic polymers designed to entrap an active ingredient [32]. The particles protect the entrapped compound from degradation and are generally more stable than liposomes. The technology allows for prolonged drug delivery that leads to increased transdermal penetration without overloading of the epidermis [32]. Consequently, less product is left on the skin surface, leading to reduced irritancy and side effects. In addition, microsphere formulations have enhanced the stability of tretinoin, a particularly unstable molecule that can be degraded when used in combination with BPO or when exposed to UV radiation [33, 34]. Although microsphere technology has been available in acne treatment for over a decade, research continues to improve on this technology.

In a recent study 0.04 % tretinoin microsphere gel was associated with fewer episodes of dryness and erythema than 0.1 % tretinoin microsphere gel [35]. Both gels represent different concentrations of the product Retin-A Micro® microsphere (Johnson & Johnson, New Brunswick, New Jersey). The 0.04 % tretinoin gel was also formulated into a pump and evaluated in a blinded, randomized split-face study of 170 acne patients. Results showed a decrease in the irritation potential of 0.04 % tretinoin microsphere gel in a pump form when compared to adapalene 0.1 % + BPO 2.5 % [36]. The pump microsphere formulation was associated with significantly less erythema, burning, and itching than the adapalene + BPO combination.

Microsphere technology has also proved beneficial in the design of BPO creams and washes. In an investigator-blinded, randomized, multicenter study comparing BPO 5.5 % microsphere cream (NeoBenz® Micro, SkinMedica, Carlsbad, California) to BPO 6 % gel, the microsphere cream demonstrated a greater reduction in noninflammatory and total lesion counts, although the results were not statistically significant [37]. Tolerability scores were significantly better for the BPO microsphere cream than the standard gel. Microspheres have also been effective in treating “facial shine,” an oily appearance to the skin, which is a common

Table 1 Recent RCTs on topical combination acne therapies: December 2010 to December 2011

Study	Drug combination	Study design	Study length	Study size (n)	Results	Tolerability and AEs
Draelos [89] ^a	CTG + BPO 4 % wash vs CTG + SFC	Randomized, single-blind study	4 weeks	61	Local tolerability reactions were slightly higher in CTG + BPO group within week 1 but improved by week 2	CTG + BPO wash appears to be well tolerated, with minimal AEs
Babayeva et al. [90]	SA 3 % + CLNP 1 % lotion vs all-TRA 0.05 % cream + CLNP 1 % lotion	Prospective, single-blind, randomized, and comparative clinical study	12 weeks	46	Both combinations were effective in decreasing inflammatory, noninflammatory, and TL counts. TL counts decreased significantly faster in the all-TRA + CLNP group.	Mild to moderate, transient AEs present in both groups
Pazoki-Toroudi et al. [91] ^a	Aza 5 %—CLIN 2 % gel vs monotherapy of Aza 5 % or CLIN 2 % gel	Multicenter, randomized, and double-blind study	12 weeks	150	Aza—CLIN gel significantly reduced TL counts and improved patient satisfaction scores when compared to either monotherapy	No significant AEs among any group
Poulin et al. [92] ^{ab}	Adapalene 0.1 % -BPO 2.5 % gel vs vehicle	Multicenter, double-blind, randomized controlled study	24 weeks	243	Adapalene—BPO gel demonstrated efficacy and improved time to relapse vs vehicle	AEs were rare in both groups
Tanghetti [93] ^b	Dapsone 5 % gel + tazarotene 0.1 % cream vs monotherapy of tazarotene 0.1 % cream	Multicenter, single-blind, randomized parallel-group study	12 weeks	171	Dapsone + tazarotene showed a greater reduction in noninflammatory and TL counts than monotherapy at 12 weeks	AEs were limited to local cutaneous reactions in both groups
Wilhelm et al. [94]	NADI 1 % cream, adapalene 0.1 % cream, BPO 5 % cream, Aza 20 % cream, or isotretinoin 0.05 % cream monotherapy vs each in combination with NADI 1 %	Single-center, phase 1, randomized, double-blind (observer-blind) study, with intraindividual comparison	3 weeks	40	Each monotherapy and combination treatment showed a mean irritation score of <1, with most scores close to 0	Both therapies showed very mild or no AEs
Choudhury et al. [95]	NADI 1 % + BPO 2.5 % vs CLIN 1 % + BPO 2.5 %	Randomized, assessor-blinded, controlled trial	8 weeks	84	NADI + BPO showed significant reduction of inflammatory lesions vs CLIN + BPO	No significant differences in the incidence of AEs reported between groups
Schmidt et al. [96] ^a	CLNP 1.2 %—tretinoin 0.025 % gel vs monotherapy of CLNP 1.2 % gel	Randomized, double-blind, multicenter, parallel study	12 weeks	2,010	Noninflammatory, inflammatory, and TL counts were more significantly decreased with combination therapy	Both treatments were well tolerated, with mild AEs such as erythema and scaling
Eichenfield et al. [97] ^a	CLNP 1.2 %—BPO 3 % gel vs monotherapy of CLNP 1.2 % gel or BPO 3 % gel or vehicle	Phase 3, multicenter, randomized, double-blind, active- and vehicle-controlled study	12 weeks	1,319	CLNP—BPO group showed superior efficacy in treating inflammatory and TL compared with monotherapy or vehicle alone	Incidence of AEs were low with no significant differences among groups
Kobayashi et al. [98]	Adapalene 0.1 % gel + NADI 1 % cream vs adapalene 0.1 % gel monotherapy	Randomized study	8 weeks	50	Adapalene gel + NADI cream produced a significantly higher reduction in inflammatory lesions at 2 and 8 weeks	Adapalene monotherapy produced more severe burning and dryness than combination treatment

AEs adverse effects, Aza Azelaic acid, BPO benzoyl peroxide, CLIN Clindamycin, CLNP clindamycin phosphate, CTG clindamycin phosphate 1.2 %—tretinoin 0.025 % gel, SFC soap-free cleanser, SA salicylic acid, all-TRA tretinoin, TL total lesions, NADI Nadifloxacin

^a Fixed-dose combination trial

^b Antibiotic-free combination trial

concern for many acne patients. Microsphere formulations of BPO and tretinoin were shown in separate split-face studies to reduce facial shine and associated sebum accumulation in the skin of acne patients [38•, 39].

Solid Lipid Nanoparticles

SLNs are solid, submicronic particles capable of carrying lipophilic and hydrophilic drugs [40]. Initially, the encapsulation of retinoids into SLN was a challenge due to retinoid instability. However, several recent advances have improved on this technology. A study published in 2011 used ion pairing between all-trans retinoic acid (atRA) and a lipophilic amine to improve the encapsulation process. In a rhino mouse model, the ion paired atRA-loaded SLNs demonstrated similar comedolytic effects and epidermal thickening to both 0.01 % atRA gel and 0.05 % atRA cream [41•]. Furthermore, the RA-loaded SLN more significantly reduced RA-induced erythema and scaling when compared to the conventional formulations.

Another encapsulation process using chitosan is being investigated. Chitosan is a biopolymer with bioadhesive and antibacterial activity [42]. A recent in vitro study of RA-chitosan loaded SLN demonstrated high physical stability over a 1-year period, high encapsulation efficiency, and high antibacterial activity against *P. acnes* [42]. Research into the use of SLNs is ongoing, and dermatologists are likely to see the development of even more cutting-edge technologies in the years to come.

Unique Formulations

Particle size plays a key role in effective acne treatment as smaller particles can better penetrate the PSU. Recently, a micronized formulation of 0.05 % tretinoin gel, known as Atralin® (Coria Laboratories, Fort Worth, Texas), has become available [43]. This low-concentration medication is comprised of micronized particles, with most of the particles less than 10 μm . The particles are also suspended in a hydrogel, allowing for regulated drug release and enhanced moisturizing capacity. [43] A post hoc analysis of 299 adolescents with mild to moderate acne compared the efficacy and tolerability of 0.05 % micronized tretinoin gel to 0.1 % tretinoin gel microsphere [43]. The micronized tretinoin gel and tretinoin gel microsphere demonstrated comparable lesion reduction, but micronized tretinoin gel displayed enhanced tolerability.

A nonprescription product combining a micronized 5.5 % BPO and 0.4 % micro-exfoliating lipophilic derivative of salicylic acid (LHA), known as Effaclar Duo® (La Roche-Posay, France), has recently come to the market. The micronized BPO particles are designed to penetrate deep into the PSU with limited exposure to the skin surface, thereby

theoretically decreasing irritation. Salicylic acid is an effective comedolytic agent, and in vitro studies show this new LHA derivative has six times the keratolytic action of salicylic acid.

Azelaic acid (AzA) is a naturally occurring dicarboxylic acid with anti-inflammatory and antimicrobial effects that has been used for several decades in the treatment of acne. Recently, a new formulation of AzA complexed with niacinamide and glycerin, known as AzaClear® (Epikinetics Pharma, Los Angeles, California), has been developed for the treatment of acne vulgaris. Niacinamide appears to enhance treatment effects, whereas glycerin acts as an emollient.

A novel drug formulation, APDDR-0901, was recently developed in Korea to improve the side effects and efficacy of retinol. A 0.03 % retinol was complexed with a 0.7 % rose extract and a 0.05 % hexamidine diisethionate cream. Hexamidine diisethionate has been shown to be active against *P. acnes* [44], whereas rose extract is thought to have anti-inflammatory effects. A double-blind RCT compared the APDDR-0901 formulation to 0.1 % adapalene gel [45]. Results showed similar efficacy between medications. However, the APDDR-0901 demonstrated significantly fewer cases of erythema, scaling, and burning than the adapalene gel.

Acne located on the back or chest is referred to as truncal acne and is a common presentation of acne vulgaris [46]. Truncal acne can be challenging to treat, as the large surface area makes topical medications more difficult to apply [46]. In a recent study, a BPO 5.3 % emollient foam (BenzE-Foam®, Onset Therapeutics, Cumberland, Rhode Island) was evaluated in patients with *P. acnes* on their backs [46]. Twenty subjects were treated once daily with BPO 5.3 % emollient foam for 2 weeks and received no treatment in week 3. In the last 2 weeks of the study, patients used a BPO 8 % wash on their backs. *P. acnes* cultures were taken after each week, with results showing a significant reduction in *P. acnes* counts after the first 2 weeks of the BPO 5.3 % emollient foam. There was no change in *P. acnes* counts in the last 2 weeks when the BPO wash was used. The authors suggest the emollient foam acts as a “leave-on” formula that permits longer contact between the skin and BPO with increased penetration of the PSU [46]. Of note, however, there are a number of cleansers that demonstrate the property of “substantivity,” meaning that BPO can persist on the skin long after the formula has been rinsed off.

Combination drug treatments, novel drug delivery systems, and unique formulations provide new and exciting alternatives to topical acne treatment. Many of these recent additions to dermatologists' acne armamentarium target multiple pathophysiologic processes in acne, reduce the complexity of treatment regimens, and improve tolerability. Novel drug combinations and

formulations will continue to develop as new advances in vehicle technology are identified.

Systemic Antibiotics

Systemic antibacterials are indicated for the treatment of moderate to severe inflammatory acne and for patients who do not respond to topical acne treatments [2•, 47, 48]. Oral antibiotics are commonly administered in combination with topical medications like a retinoid and/or BPO to enhance therapeutic efficacy and decrease emergence of *P. acnes* resistance. Tetracyclines are the antibiotic class prescribed most frequently for the treatment of acne. Tetracyclines are bacteriostatic, and their mechanism of action involves the inhibition of *P. acnes* proliferation within the sebaceous follicles, as well as an independent anti-inflammatory effect [6, 49–51]. Of the tetracyclines, doxycycline and minocycline are used most often because of their increased efficacy and decreased association with *P. acnes* resistance [52].

Minocycline is the most lipophilic of all the tetracyclines, thus increasing its ability to penetrate the lipid-rich sebaceous follicles [53]. The lipophilic nature of minocycline also enhances its absorption, making its ingestion less cumbersome than other tetracyclines, as it is less affected by food or dairy intake [54•]. Minocycline has also been associated with decreased bacterial resistance as compared to the other tetracyclines [55, 56]. Minocycline's enhanced lipophilicity not only improves its efficacy in acne treatment but also increases its ability to cross the blood–brain barrier leading to acute vestibular adverse events [57]. Solodyn® (Medicis, Scottsdale, Arizona) is an extended-release formulation of minocycline that has been able to decrease the existence of these adverse effects while maintaining the efficacy of minocycline immediate release. Solodyn's reduction in adverse drug reactions is related to its delayed time to peak plasma concentration (Tmax) and reduced peak plasma concentration (Cmax) [53]. Rapid absorption and/or high-peak concentrations of a medication may induce or exacerbate adverse drug reactions [58]. Studies assessing the weight-based dosing of Solodyn demonstrate that a dose of 1 mg/kg/day was as effective as 2 mg/kg per day and 3 mg/kg per day with a significant decrease in adverse effects, especially acute vestibular effects. [57, 59]. In 2006, the Food and Drug Administration (FDA) approved Solodyn for the treatment of non-nodular moderate to severe acne.

Some tetracyclines are associated with other adverse reactions, including gastrointestinal distress and vaginal candidiasis [60•]. To prevent vaginal yeast infections, the authors suggest eating yogurt with live cultures or taking probiotics throughout the course of antibiotic treatment. Probiotics not only ameliorate the side effects of antibiotics but may

decrease systemic levels of inflammation and regulate inflammatory cytokines in the skin [61]. Minocycline has also been associated with an increased risk of hyperpigmentation and systemic immunologic reactions including hypersensitivity and lupus-like syndromes with several reports present in the literature [54•]. It is unclear as of yet what Solodyn's role may be in exacerbating or reducing these specific adverse drug reactions [54•].

Antibiotic Resistance: A Growing Concern

Antibiotics used to be at the forefront of acne treatment and frequently used as monotherapy. However, antibiotic resistance has resulted in a decline in their therapeutic efficacy. Long-term use of antibiotics (both systemic and topical) produces selection pressure, which leads to the proliferation of antibiotic-resistant bacteria [62•]. Long-term antibiotic use not only translates into decreased efficacy but also far-reaching deleterious effects such as an increased risk of developing infections [62•]. Margolis et al. [63] showed that the odds of an upper respiratory tract infection in a patient receiving long-term antibiotics for acne was 2.15 times greater than those acne patients not receiving antibiotics. Furthermore, in a recent prospective study, patients receiving oral antibiotics for acne had three times the odds of developing pharyngitis than patients who were not taking antibiotics [64].

Long-term antibiotic use in acne has also been associated with the development of resistance in bacteria other than *P. acnes*, including coagulase-negative staphylococci (CNS) [65, 66]. This is particularly concerning as antibiotic-resistant CNS can serve as a reservoir of antibiotic resistance genes and spread to other bacteria and hosts [62•, 67]. It is possible for these antibiotic-resistant genes to be transferred to more severe pathogenic organisms such as *Staphylococcus aureus* (*S. aureus*) [62•, 68]. These findings suggest the importance of limiting the use of antibiotics to the shortest duration and dosage necessary, and using combination therapy with BPO to slow the development of resistance.

Because of the growing concern of antibiotic resistance, antibiotic-free therapeutic options for the treatment of acne are increasing in popularity. Among the trials listed in Table 1, two demonstrate the effectiveness of antibiotic-free topical combination treatments. One of these studies includes a fixed dose combination of the adapalene 0.1 % and BPO 2.5 % (Epiduo®, Galderma, Fort Worth, Texas). Although, BPO is effective against proliferation of *P. acnes*, there has been no evidence to date of *P. acnes* resistance to BPO. A 2011 open-label, single-center study by Leyden et al. [69•] demonstrated the effectiveness of adapalene 0.1 % and BPO 2.5 % gel on antibiotic-sensitive and resistant *P. acnes*. In fact, the combination gel reduced strains of antibiotic-resistant and antibiotic-sensitive bacteria by 97 %. The decreased therapeutic efficacy

of antibiotics against resistant *P. acnes*, as well as the global health impact of antibiotic resistance, makes nonantibiotic medications enticing options for dermatologists.

Novel Topical and Oral Acne Medications

Topical Dapsone

Among the most novel drugs available for acne treatment is dapsone 5 % gel. Oral dapsone is an anti-inflammatory and antimicrobial medication used for the treatment of a number of skin disorders, but its increased side effect profile prevented its use in acne treatment [70•]. A topical form of dapsone has recently been approved for the treatment of acne vulgaris, based on two randomized, vehicle-controlled studies [71]. Topical dapsone was also found to have a desirable side effect profile over the long-term in a 12-month safety and efficacy trial [72]. Moreover, the pharmacokinetics of the gel were examined in two separate studies [73]. Topical dapsone has been extensively studied and its safety confirmed; however, its efficacy appears to be modest in recent clinical trials. In practical application, dapsone appears to reduce the irritation of topical retinoids and contributes significantly to their efficacy.

Oral Antifungals: A New Direction for Acne Treatment?

P. acnes is not the only organism present in acne. In an article published by Leeming et al. [74], it was reported that *Malassezia* organisms were found in 68 % of 3-day old acne papules. The report was documented over 20 years ago, but researchers only recently have attempted to target this organism in treatment [4••]. The effects of azole antifungals on acne are multidimensional, as these medications are not only effective as antifungals but active against *P. acnes* [75••]. A study by Sugita et al. [75••] showed in vitro efficacy of miconazole, ketoconazole, and itraconazole against antibiotic-sensitive and antibiotic-resistant strands of *P. acnes*. Moreover, azole medications are known to have anti-inflammatory effects [76] that may further add to their effectiveness in acne therapy [4••].

Hormonal Antiandrogens in Acne

It has long been known that the activation of androgen receptors leads to increased sebum production and plays a key role in acne pathogenesis. Oral contraceptives and spironolactone are the primary antiandrogenic treatments used in women with polycystic ovarian syndrome, hyperandrogenism, and premenstrual acne flares [60•]. Although spironolactone is not approved by the FDA for the treatment of acne, it is often prescribed off label [60•]. In the authors'

opinion, adult females who present with acne primarily on the lower face respond well to spironolactone, even in the absence of hormonal dysregulation. Drospirenone-containing oral contraceptives are also particularly effective in controlling acne, as drospirenone is a progestin with no androgenic capacity [4••, 77].

Some topical hormonal agents show promise for the treatment of acne but are not yet available. Cortexolone 17 α -propionate is a new steroidal antiandrogen topical cream under development for the treatment of acne. In a recent pilot randomized, double-blind study, cortexolone 17 α -propionate was found to significantly reduce total lesion counts and inflammatory lesion counts to a greater extent than topical tretinoin 0.05 % cream and placebo. [78]. Although this trial was limited in scope, it may stimulate future studies using topical antiandrogens in the treatment of acne. Another topical agent in development for the treatment of acne is nestorone, a nonandrogenic progestin combined with ethinyl estradiol [4••, 79].

As mentioned earlier, melanocortins and melanocortin receptors (MC1R–MC5R) have been shown to play a role in sebogenesis [17–19]. Moreover, it is known that MC1R is expressed in several cell types of human skin, and MC5R is expressed in human sebaceous glands [17]. A novel MC1R and MC5R antagonist (JNJ-10229570) for the topical treatment of acne is currently being investigated. Results of a recent study of the topical MCR antagonist demonstrated marked reduction in sebum gland size and sebum-specific lipid production in human skin transplanted to mice with severe combined immunodeficiency [80••].

A Changing Paradigm: Diet and Acne

The link between diet and acne has presented much controversy over the years [81•]. Recently, researchers have revisited the link with particular attention to the role of dairy products (in particular skim milk) and high-glycemic load diets [81•]. Although the strongest evidence to date focuses on these two dietary influences, some preliminary studies suggest that antioxidants, fish oil, and probiotics may also play a role in acne [61, 82].

Procedural Treatments for Acne

Procedural treatments such as light and laser therapy are gaining popularity in the treatment of acne. These treatments are particularly attractive to patients as they represent cutting-edge alternatives to conventional acne treatments [83]. The following sections discuss some of the most recent research on these technologies.

Lights and Lasers

P. acnes produces photoactive substances called porphyrins that when exposed to visible light produce reactive oxygen species that are toxic to the bacteria [84]. In addition to these antimicrobial effects, blue light has also been shown to have anti-inflammatory properties [85]. Recently, at-home devices using red or blue light have become popular among patients. A recent randomized self-control study of home-use blue-light therapy demonstrated significant improvement in acne lesions as compared to placebo [86]. Photodynamic therapy is the technique of introducing exogenous porphyrins into the skin that can then be activated by light [83]. A recent study suggests this procedure works by downregulating TLR-2 and TLR-4 expression in the epidermis and sebaceous glands of patients with acne [87]. As discussed earlier, the activation of TLRs is thought to play a key role in the pathogenesis of acne [5].

Photopneumatic Therapy

Photopneumatic therapy is a device using negative pressure applied as suction with delivery of broadband, pulsed light. It is the only laser or light therapy approved by the FDA for acne [83]. The authors (Bowe and Shalita) have conducted the first RCT evaluating the efficacy of this therapy [88]. This study examined the effectiveness of Isolaz® (Solta Medical, Hayward, California), a photopneumatic device that combines vacuum pressure with a broadband light source (400–1,200 nm). Thirty-seven patients were randomized to receive vacuum therapy alone or in combination with broadband light. Inflammatory and noninflammatory lesions were decreased in both groups, with no significant difference between groups. The results indicate that both pneumatic therapy and photopneumatic therapy is effective in the treatment of acne. It is thought the mechanical disruption of biofilms in the PSU combined with evacuation of follicular contents is the primary mechanism of action of photopneumatic therapy.

Conclusion

Acne vulgaris is an extremely common skin condition, resulting in significant physical and emotional morbidity. Currently, the treatment of acne primarily includes the use of topical and oral medications. Fixed-dose topical drug combinations have been shown to be most effective in the treatment of mild to moderate acne, as they improve therapeutic efficacy, reduce side effects, and promote patient adherence. Although antibiotic treatment remains a key tool in acne therapy, increasing concerns regarding antibiotic resistance have lead dermatologists to reduce the dosage

and length of antibiotic therapy. Additionally, new drug regimens that do not include antibiotic therapy are growing in popularity, including the use of nonantibiotic combination therapies, antifungal agents, and hormonal modulators. The role of diet has also become a popular discussion among dermatologists, with intriguing research demonstrating the negative effects of certain dairy products and high-glycemic load diets on acne. Finally, research into procedural treatments for acne continues with the need for more clinical trials to truly elucidate the value of these therapies. As the field of dermatology continues to gain insights regarding acne pathogenesis and combine this knowledge with cutting-edge delivery mechanisms, options for treating acne will amplify.

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