

An update on the pharmacological management of acne vulgaris: the state of the art

Isabel Cristina Valente Duarte de Sousa

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REVIEW



An update on the pharmacological management of acne vulgaris: the state of the art

Isabel Cristina Valente Duarte de Sousa

Department of Dermatology, Centro Medico ABC, Mexico City, Mexico

ABSTRACT

Introduction: Acne vulgaris is a chronic inflammatory disease of the pilosebaceous unit that affects approximately 9.4% of the global population. Current treatment strategies aim to target as many pathogenic factors involved in the appearance of acne lesions and are centered on a systematic treatment escalation based on disease severity, extension, and treatment response, starting with topical treatments for mild cases and progressing over to systemic therapies in more severe cases. A literature search, which included clinical guidelines, clinical studies, and review articles on acne treatment and maintenance, was conducted to review the pharmacological approaches currently available to treat this disease.

Areas Covered: Topical therapies such as topical retinoids, benzoyl peroxide, azelaic acid, salicylic acid, topical antibiotics, and clascoterone, as well as systemic treatments such as oral antibiotics and isotretinoin are discussed in detail. Combined oral contraceptives and spironolactone will not be discussed in this article.

Expert Opinion: There is a need for a blockbuster acne drug that simultaneously targets the four main pathogenic factors involved in the appearance of acne lesions while presenting with minimal side effects. Until such a drug exists, combination therapy will remain the standard of treatment for most acne patients.

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1. Introduction

Acne vulgaris is a chronic inflammatory disease of the pilosebaceous unit [1,2] that affects approximately 9.4% of the global population, making it the eighth most prevalent disease worldwide and the most common skin conditions diagnosed and treated by dermatologists [3]. Although acne is present mainly in teenagers, affecting about 85% of them, it can persist into adulthood [3]. Four main interrelated pathogenic factors, that act synergistically in a complex manner are involved in the development of acne lesions: 1. Increased sebum production due to androgen-driven sebaceous gland hyperplasia; 2. Hyperkeratinization of the follicular epithelium due to abnormal follicular growth and differentiation; 3. Colonization of *Cutibacterium acnes* (*C. acnes*) within the pilosebaceous unit; and 4. Activation of innate and acquired immunity followed by the release of inflammatory mediators into the skin [1,2,4]. In addition, other elements such as neuroendocrine regulatory mechanisms, genetics, diet (namely a high glycemic index diet and dairy intake), the microbiome and environmental factors may contribute to this multifactorial process [5–7].

Although in most cases acne vulgaris is a self-limiting disease, it can take several years for it to naturally resolve [8]. Furthermore, regardless of its severity, acne may be associated with long-lasting side effects, such as hyperpigmentation, and scarring [1,2,4,9,10]. Patients with acne may also experience depression, anxiety, low self-esteem,

diminished quality of life and even suicidal ideations [11,12]. Acne, therefore, imposes a considerable burden on those affected by the disease [12,13], as measured by disability-adjusted life years, which ranked acne the second most burdensome skin diseases in 2013 [14]. Early diagnosis and treatment are, therefore, of utmost importance [15].

Current treatment strategies aim to target as many pathogenic factors involved in the development of acne lesions and are centered on a systematic treatment escalation based on disease severity, extent, and treatment response, starting with topical treatments for mild cases and progressing over to systemic therapies in more severe cases [1,2,4,9,10,15–18]. This article discusses the pharmacological approaches currently available to treat this disease. This article does not address specific clinical situations such as infant or pediatric acne, adult female acne, hormonal acne, acne associated with syndromes, acneiform eruptions, and medication-induced acne. A comprehensive literature search was conducted in PubMed and Google Scholar using the keywords ‘acne treatment,’ ‘acne therapy,’ ‘acne pharmacological treatment,’ and ‘acne pharmacological therapy.’ International clinical acne guidelines, expert consensus, clinical studies, and review articles on acne pharmacological treatment and maintenance were included in this review. Studies testing light devices or procedures such as microdermabrasion and chemical peels were excluded.

Article highlights

- Minocycline foam, the first topical minocycline available on the market, could potentially have a lower incidence of antibiotic resistance compared to clindamycin and erythromycin.
- Sarecycline, the newest tetracycline approved exclusively for the treatment of acne vulgaris, has a narrow-spectrum activity against *C. acnes*, which translates into low propensity for inducing bacterial resistance and may possibly result in reduced dysbiosis.
- Trifarotene, the newest topical retinoid available, could potentially decrease adverse effects associated with topical retinoid use without negatively impacting effectiveness. Clascoterone, a first of its kind topical antiandrogen, is safe for use in both males and females due to its low systemic absorption and thus could be an interesting addition to the treatment arsenal available for acne vulgaris.
- Benzene present in benzoyl peroxide products poses a concern regarding the safety of such products in the treatment of acne.
- New strategies for controlling *C. acnes* population without the risk of negatively impacting the microbiome are being currently researched.

2. Topical therapies

Topical therapies (Table 1) are the foundation of acne treatment as they are used during the initial treatment as well as during maintenance therapy. These include topical retinoids, benzoyl peroxide (BP), azelaic acid, salicylic acid, topical antibiotics, and clascoterone. When managing acne with topical therapies, multimodal therapy combining multiple mechanisms of actions is recommended to optimize efficacy and to reduce the risk of antibiotic resistance [16].

2.1. Topical retinoids

Topical retinoids (adapalene [19–21], tazarotene [22,23], tretinoin [24,25], isotretinoin [26], and trifarotene [27–29]), the mainstay of acne treatments [30], are vitamin A derivatives that have anti-inflammatory, comedolytic, and anti-comedogenic properties [31–33]. Retinoids exert their anti-inflammatory properties by decreasing neutrophil chemotaxis, decreasing leucocyte migration, blocking Toll-like receptor

expression, inhibiting the AP-1 pathway, and reducing the release of reactive oxygen species and of inflammatory cytokines into the skin [31–33]. Furthermore, retinoids modulate keratinocyte adhesion molecules and regulate the differentiation and proliferation of keratinocytes consequently inhibiting microcomedo and comedo formation [20,31–33]. Microcomedos, the clinically invisible precursor of all other acne lesions, can be present even in normal-looking skin [20,31–33]. Therefore, retinoids not only help treat active disease but also prevent the development of new acne lesions [2,20,31,32], allowing for maintenance of clearance after successful treatment [9]. Topical retinoids are also able to enhance the penetration of other topical acne medications [31].

Topical retinoids show the most robust evidence against comedos and microcomedos [2,10,20], leading to the perception that these agents should primarily be used for comedonal acne [30]; however, monotherapy with these medications also significantly reduces papules, pustules, and cysts [9,19], with an effect that is comparable to that of ‘non-inflammatory’ lesions [34–36]. Therefore, topical retinoid-based therapy is recommended as a first-line approach for almost all acne patients by the Global Alliance to Improve Acne Outcomes and all major international clinical guidelines and expert consensus [2,4,9,10,15,16,18]. Although each retinoid binds to a different set of retinoic acid receptors and confers modest differences in activity, tolerability, and efficacy [16], existing comparative effectiveness data do not suggest superiority of one topical retinoid against another [31]. Therefore, in mild acne vulgaris, any of the available topical retinoids are suitable to use as monotherapy [2,4,9,10,15,16,18]. Nonetheless, adapalene is usually preferred over tretinoin [10,31], isotretinoin [10], and tazarotene [15,31] because of its better tolerability profile [31,37], which could lead to a better adherence to treatment [31]. Tretinoin, however, seems to be faster in reducing inflammatory lesions than other topical retinoids, which, in turn, could potentially increase patient satisfaction [31]. Trifarotene, the most recent retinoid approved for the treatment of acne, is a topical fourth-generation retinoid selective for retinoic acid receptor

Table 1. Topical therapies for acne management.

Drug	Main mechanism of action	Secondary Mechanism of action	For use in which type of acne?	Good for Maintenance Treatment?	Comments
Topical retinoids	Comedolytic and anti-comedogenic	Anti-inflammatory	All, except nodular, conglobate or cystic acne	Yes	Not for use during pregnancy or lactation
Benzoyl Peroxide	Bactericidal agent	Mild comedolytic effect	All, except exclusively comedonal acne	Yes	Great alternative to topical antibiotics as it causes no bacterial resistance
Azelaic acid	Anticomedonal and anti-inflammatory	Bacteriostatic and antioxidant properties	Patients that do not tolerate topical retinoids or pregnant/breastfeeding patients	Yes, especially in patients with post-inflammatory hyperpigmentation	Good for hyperpigmentation Safe during pregnancy and lactation
Salicylic acid	Comedolytic	Anti-inflammatory	Patients that do not tolerate topical retinoids	Yes	Available over the counter
Topical antibiotics	Bactericidal agent	Anti-inflammatory	Mild Inflammatory acne	No	Should not be used in monotherapy or for long periods of time due to risk of bacterial resistance
Clascoterone	Anti-androgen that modulates sebum production	—	All	Maybe, more data needed	Expensive More data needed on its use combined with other treatments

(RAR)- γ [27–29] with more than 20-fold higher selectivity at RAR γ than at RAR α and RAR β [29]. RAR γ is the most common isoform of RARs in the skin, and the strong selectivity of trifarotene for RAR γ translates to efficacy in low concentration [27]. Trifarotene could potentially limit adverse effects linked to RAR agonism [29] and therefore be better tolerated by patients presenting as a better treatment option than first-generation retinoids (tretinoin) that bind to all three RARs (RAR α , RAR β , and RAR γ), and than third-generation retinoids (adapalene and tazarotene) that bind preferably to RAR α and RAR γ [29]. Furthermore, trifarotene is the first topical retinoid with rigorous clinical data on safety and efficacy in truncal acne [27,28], while all other retinoids have mostly been studied focusing on face acne exclusively. Approximately 50% to 66% of the individuals with acne have trunk involvement [38,39], which confers trifarotene an advantage over other retinoids.

For more severe forms of acne, higher concentrations of the topical retinoid and/or combining it with antimicrobial agents, benzoyl peroxide (BPO) [40], topical antibiotics, and/or oral antibiotics are more important than the type of topical retinoid used in improving disease severity [16]. Dose-dependent increases of topical retinoids lead to greater efficacy [19,21], however, higher concentrations also tend to be more irritating than lower concentrations [16,37]. Adverse effects of topical retinoids include skin sensitivity, burning sensation, dryness, irritation, erythema, peeling, pain, and exfoliation [15,22,25,31,41], which could reduce adherence to treatment and impact therapeutic outcomes. The frequency of clinical irritation is generally low with all topical retinoids, and skin irritation is typically observed within the first few weeks of treatment and then subsides [37]. To ensure better tolerance, some patients require alternate regimens of topical retinoids, a reduction in concentration or application frequency [31,32] the concurrent use of emollients [42,43], or different topical formulations as it has been shown that retinoids in a foam vehicle are better tolerated than their gel counterpart [23]. Retinoids are contraindicated in pregnant and breastfeeding patients [44,45] and so other topical therapies are preferred during pregnancy even though there are no human studies that have established a causal relationship between the use of topical retinoids with birth defects [16].

2.2. Benzoyl peroxide

Benzoyl peroxide (BPO) is an over-the-counter [16] topical bactericidal agent that exerts its antibacterial effect through the production of benzoic acid and the release of reactive oxygen species (ROS) [46]. ROS oxidizes bacterial proteins, thus inhibiting bacterial nucleotide synthesis, metabolic pathways, and mitochondrial activity [47]. In patients with acne, this translates into the suppression of preexisting resistant strains of *C. acnes* while limiting the development of new resistant strains during topical antibiotic use [48]. To date, no bacterial resistance to BPO has been reported [16,46] making it a good alternative to topical antibiotics in acne. Due to its lipophilic properties, BPO concentrates inside the sebaceous follicles [47–49] and has been shown to exert mild comedolytic effects [47,49,50]. Furthermore, BPO also shows anti-

inflammatory properties by decreasing the levels of proinflammatory-free fatty acids [47,49,50].

BPO monotherapy has a similar [51,52], if not superior [53], efficacy to topical isotretinoin and tretinoin against inflammatory lesions [51–53] and is comparable in efficacy and tolerability to adapalene in patients with mild acne [54–56]. Therefore, BPO is one of the standards of care for mild-to-moderate papulopustular acne [2,4,9,10,15,16,18]. Common side effects include irritation and erythema [46,47,49]; which are more common with increasing concentrations, so lower concentrations of BPO (2.5%) are preferred as there is no significant increase in efficacy with higher concentrations (5% and 10%) [47,49,50]. BPO can also discolor clothes [46] which should be discussed with patients.

In March 2024, Valisure LLC, an independent U.S. testing laboratory, found high levels of benzene, a known carcinogen, in various benzoyl peroxide acne products [57]. The FDA's guidelines specify that there is no safe level of benzene exposure to humans and as such, drug products should not contain benzene because of its unacceptable toxicity [57]. Nonetheless, the FDA does allow up to 2 parts per million of benzene in products, only if benzene is absolutely necessary to manufacture said products [58]. Valisure, however, found that some acne benzoyl peroxide products contain up to 12 times the allowed amount, and that the parts per million of benzene found in these products intensify with increasing temperatures [57]. Importantly, benzene found in BPO products is due to degradation of BPO rather than contamination of the product [58]. In the presence of heat, BPO decomposes to form benzoyloxy radicals that can further decompose to benzoic acid or phenyl radicals. The phenyl radicals can then produce end products such as benzene, phenyl benzoate, and biphenyl, depending on the chemical environment [59]. The significance of these findings in humans is currently unknown and more studies are needed to determine the long-term safety of BPO containing products.

BPO is available in a variety of preparations including gels, washes, lotions, and creams. There is no clear superiority of these different preparations in terms of effectiveness [46,49] and water-based and wash-off formulations may be better tolerated [50]. In patients who are pregnant, the risk of fetal harm from topical BPO was previously not expected based on limited systemic absorption [44,45]; however, the new information available on benzene present in BPO products [57,58] should be taken into consideration.

2.3. Azelaic acid

Azelaic acid exhibits mild anticomedonal attributes, as well as bacteriostatic, anti-inflammatory [60,61], and antioxidant properties [61], thus reducing the severity of acne [62] and conferring an useful alternative in treating mild inflammatory acne [1,2,4,8–10,15,16]. Azelaic acid shows a comparable efficacy to tretinoin, adapalene, and benzoyl peroxide [63] for inflammatory acne with a better tolerability and safety profile [10,63], making it useful in patients with sensitive skin [2,4] or those who do not tolerate topical retinoids or benzoyl peroxide. Furthermore, it has a lightening effect on dyspigmentation, so patients with darker skin tones may find it particularly

helpful [64]. Furthermore, azelaic acid is safe for use during pregnancy and breastfeeding and so it represents an important option for women of childbearing age and with a desire to become pregnant [44,65]. Treatment with azelaic acids also shows high patient satisfaction rates [65] which could positively impact treatment adherence.

2.4. Salicylic acid

Salicylic acid (SA) promotes individual corneocyte desquamation [17,42] and thus, exhibits comedolytic properties making it moderately effective in the treatment of comedonal acne when used in monotherapy [42,66]. In one randomized controlled trial, SA 0.5% showed a 11% greater reduction in open comedos, no difference in closed comedos and a 25% greater reduction in inflammatory lesions when compared to vehicle at 12 weeks [67]. It shows a similar tolerability profile to BPO gel and so it can be considered as a third-line treatment option [4,16] for mild inflammatory acne, especially in patients who cannot tolerate topical retinoid therapy [16]. Salicylic acid is safe to use during pregnancy if the area of exposure is small and the duration of therapy is limited; use for large areas or under occlusion is not recommended due to the potential for systemic absorption [45]. SA is available over the counter with concentrations ranging from 0.5% to 2% [16].

2.5. Topical antibiotics

Topical antibiotics (erythromycin, clindamycin, minocycline, and dapsone) exert their anti-acne effect through antibacterial and anti-inflammatory action [48,68,69]. Compared to vehicle alone, topical antibiotics notably reduce the number of 'inflammatory' lesions (a.k.a. papules and pustules) [70–74]. Although some authors claim that topical antibiotics are also mildly effective against 'non-inflammatory' acne lesions (a.k.a. comedos) [68], most published data does not support a statistically significant reduction in these types of lesions using topical antibiotic monotherapy [70–74]. There is a lack of active comparator studies to suggest if any one topical antibiotic is superior to another [16]. Historically, the most frequently used topical antibiotics in mild-to-moderate acne were erythromycin, a macrolide antibiotic, and clindamycin [20,48,69], a lincosamide derivative [48], both of which are bacteriostatic and interact with bacterial ribosomal subunits to inhibit protein synthesis, thus reducing total *C. acnes* counts [75]. Furthermore, erythromycin and clindamycin also exhibit anti-inflammatory activity by inhibiting the chemotaxis of neutrophils [75,76], blocking complement pathways [76], and reducing the synthesis of lipase, which is then utilized by *C. acnes* for hydrolyzing serum triglycerides to glycerol and proinflammatory-free fatty acids [76].

Topical minocycline foam 4%, the first topical minocycline product available, was approved by the FDA in 2019 to treat inflammatory lesions of non-nodular moderate-to-severe acne [77]. In vitro, topical minocycline foam 4% exhibits potent antibacterial activity with a low frequency of spontaneous resistance in *C. acnes* isolates [78]. Clinical trials have shown that once-daily application of topical minocycline foam 4%, significantly reduces both inflammatory and non-inflammatory

lesions in patients with moderate-to-severe acne [70,79]. Adverse effects of topical minocycline are uncommon and are seen in less than 1% of the patients. These include yellow skin discoloration, dry skin, pruritus, facial swelling [70] application site discomfort, and yellowing of the nails [79].

Dapsone, is an antimicrobial that inhibits dihydrofolic acid through competitive inhibition of para-aminobenzoic acid at the dihydropteroate synthetase active site [80]. Dapsone gel has also been approved for the treatment of acne, and although its exact mechanism of action against inflammatory acne lesions has not been clearly elucidated, it is thought to be linked to its anti-inflammatory properties more so than its activity against *C. acnes* (which remains poorly understood) [81]. Dapsone decreases neutrophil recruitment and inhibits myeloperoxidase activity leading to anti-inflammatory effects similar to those presented by nonsteroidal anti-inflammatory drugs [80]. Topical dapsone is available in the United States as 5% and a 7.5% gel [82]. Both concentrations have shown an improvement in inflammatory lesion count when compared to vehicles [73,74,81–83]. Furthermore, topical dapsone is also effective in reducing inflammatory and non-inflammatory lesions in patients with truncal acne [84]. Common side effects include pruritus and dryness; serious side effects associated with oral dapsone are not seen with the topical formulation because of its low systemic absorption [80]. Combination of topical dapsone with topical benzoyl peroxide might produce unwanted yellow discoloration of both skin and facial hair [80].

Although topical antibiotics are effective in treating acne, the routine widespread and long-term use of topical antibiotics in the treatment of acne has resulted in antibiotic-resistant *C. acnes* and changes in the microbiome [85]. Antibiotic resistance in *C. acnes* was first reported in 1979 [86] and is now prevalent all over the world, with at least 50% of acne patients colonized with erythromycin and clindamycin resistant *C. acnes* [87]. Because of this growing *C. acnes* resistance rate to topical antibiotics, especially when used by themselves, there is a growing concern among dermatologist to limit antibiotic use [68,87], and so, current recommendations for the treatment of acne advise against antibiotic monotherapy [2,9,10,16,68,75,85,87] and suggest instead that they should solely be prescribed in combination with BPO or topical retinoids [2,4,9,10,16,75]. Furthermore, topical antibiotics should not be used for longer than 4 weeks, even in combination regimens, as resistance occurs in 3 weeks [86].

In pregnant patients, erythromycin and clindamycin are considered safe based on limited expected systemic absorption [44,45]. Topical minocycline is not recommended during pregnancy or lactation, and there is currently no data available on the safety of topical dapsone during pregnancy or lactation [16].

2.6. Clascoterone

Androgens are the main hormones that target sebaceous glands and modulate sebum [88]. Combined oral contraceptives [89] and spironolactone [90], both androgen receptor blockers, are commonly prescribed for the treatment of acne vulgaris in females due to their antiandrogenic effects [91].

These drugs are unsuitable for administration to males with acne vulgaris because of undesirable side effects such as feminization, gynecomastia, and erectile dysfunction [88]. Therefore, topical inhibition of an androgen receptor emerges as a more appealing therapeutic option for acne vulgaris management [92].

Clascoterone, a topical antiandrogen that directly binds the androgen receptor and inhibits androgen-mediated lipid and inflammatory cytokine synthesis from sebocytes [93], is the first topical acne medication that targets the hormonal factors involved in the development of acne lesions [94]. Clascoterone competes with DHT for its receptor in the skin and decreases the transcription of the androgen-responsiveness genes, thus culminating in reduction of the sebum production and proinflammatory cytokines [93,95]. Following topical application of clascoterone, it is promptly metabolized to its inactive metabolite cortexolone, thus limiting systemic absorption and development of systemic anti-androgen adverse events [93–95].

Clascoterone 1% cream was approved by the Food and Drug Administration (FDA) in 2020 as a novel therapy for the treatment of acne vulgaris in individuals aged 12 or older [94]. A recent meta-analysis and systematic review on the efficacy and safety of clascoterone 1% cream that included five high quality randomized controlled trials comprising a total of 2457 patients concluded that clascoterone cream was statistically superior to vehicle in improving global clinical assessment scores and non-inflammatory lesion count [91]. Clascoterone cream was also superior to vehicle in reducing inflammatory lesion count, however the difference was not statistically significant [91]. Furthermore, a pooled analysis of safety outcomes revealed that topical clascoterone is safe, well tolerated, and has negligible systemic anti-androgenic effects [91]. No evidence exists regarding the safety of clascoterone use during pregnancy or lactation [16,94] or its efficacy in combination with or compared to existing topical and systemic acne therapies [94].

2.7. Combination treatments

Because of their complementary mechanisms of action, combination of topical agents such as BPO/antibiotic, retinoid/BPO, or retinoid/antibiotic present synergistic effects on clinical efficacy and inflammatory markers, which results in faster

and more complete clearance of acne lesions than their individual monotherapies [2,4,9,10,17,31,54,56,96] and exceeding what would be expected from the sum of their separate efficacies [47,54,96,97]. Combination therapies can be prescribed as separate products that are used together or as fixed combination preparations that exist as a single product [10,54–56,72,98]. Fixed-dose combinations are usually less expensive and easier to use which facilitates treatment and positively impacts adherence [16,98]. Potential adverse effect profiles of the fixed-dose combinations generally reflect those of the individual agents in summation [16,97]. Fixed dose combination of clindamycin 1%/BPO 3%, clindamycin 1%/BPO 5% [10,16,72,96], clindamycin 1%/tretinoin 0.025%, adapalene 0.1%/clindamycin 1% [16,75], adapalene-0.1%/BPO-2.5% [9,10,16,55,56], adapalene-0.3%/BPO-2.5%, tretinoin-0.025%/clindamycin phosphate-1.2% [9,16], and clindamycin 1.2%/adapalene 0.15%/benzoyl peroxide 3.1% [99] are available on the U.S. market. Of note, concomitant BPO use with topical retinoids [41,56] and/or topical antibiotics [72,100] may prevent antibiotic resistance [16] and therefore should be considered for initial and maintenance therapy in patients with mild-to-moderate acne.

3. Systemic therapies

Systemic therapies (Table 2) are used in moderate-to-severe acne cases or in patients who did not respond to topical medication [2,4,9,10,15,16,18]. These include oral antibiotics, isotretinoin, combined oral contraceptives, and spironolactone [2,4,9,10,15,16,18]. Combined oral contraceptives and spironolactone will not be discussed in this article as they can only be prescribed to female subjects, due to their anti-androgenic side effects that lead to erectile dysfunction, gynecomastia, and feminization in males [88].

3.1. Oral antibiotics

Systemic antibiotics have been extensively used to treat moderate-to-severe inflammatory acne [101]. The most frequently prescribed oral antibiotics for acne and first-line choice of many international acne guidelines are tetracyclines [2,4,9,10,15,16,18,86,101]. Tetracyclines (i.e. tetracycline, doxycycline, lymecycline, minocycline, demeclocycline, and sarecycline) [102–104] exhibit both antibacterial and anti-inflammatory properties [103]. Their anti-inflammatory action

Table 2. Systemic therapies for acne management.

Drug	Main Mechanism of action	Secondary Mechanism of action	For use in which type of acne?	Good for Maintenance Treatment?	Comments
Oral antibiotics	Bactericidal agent	Anti-inflammatory	Moderate to severe inflammatory acne	No	Should not be used in monotherapy or for long periods of time due to risk of bacterial resistance
Isotretinoin	Anti-comedonal, anti-inflammatory, sebum regulating	Suppresses C acne counts by altering the microenvironment within the follicular duct	Nodular, conglobate or cystic acne Moderate to severe inflammatory acne	No	Use carefully in females of childbearing age due to teratogenic effects

is exerted by inhibiting neutrophil chemotaxis and downregulating inflammatory cytokines, such as Interleukin-1, tumor necrosis factor- α , and Interleukin-6 [103]. Furthermore, they inhibit metalloproteases, down-regulate the production of free radicals and inhibit T-cell proliferation [102–104].

The superior efficacy of one cycline over another for the treatment of acne has not yet been determined [102]; however, doxycycline, minocycline, and lymecycline are more widely used due to their longer half-life (allowing for less frequent dosing regimens), improved bioavailability and higher lipophilicity (which improves uptake into the pilosebaceous unit) [69,101]. Oral minocycline has the lowest resistance rate among *C. acnes* isolates when compared to other cyclines [87]. However, oral minocycline can cause rare, but severe, adverse vestibular events, such as dizziness, vertigo, tinnitus, and light-headedness [101,102]; therefore, doxycycline and lymecycline have been classically preferred by physicians. Sarecycline, the newest tetracycline developed, was approved by the U.S. FDA in 2018 specifically for the treatment of acne vulgaris [104]. Sarecycline has a narrow-spectrum activity toward Gram-positive bacteria such as *C. acnes*, which translates into low propensity for inducing resistance in *C. acnes* [105]. Furthermore, when compared to other cyclines, sarecycline has less activity against Gram-positive and Gram-negative bacteria that are part of the normal human microbiota [105] possibly resulting in reduced dysbiosis. Moreover, sarecycline has shown a low potential for inducing bacterial resistance [105].

As an alternative to cyclines, in patients in whom tetracyclines are contraindicated, for example, in pregnant women or in children younger than 8 years, systemic erythromycin, azithromycin, amoxicillin, or trimethoprim-sulfamethoxazole can be used [2,4,9,10,15,16,18]. However, there is some debate on which of these antibiotics should be preferred as a second-line therapy due to the lack of systematic and comparative studies [106]. Erythromycin and azithromycin are macrolide antibiotics that have been classically used to treat acne [9,16,106]. Erythromycin and azithromycin both bind to the 50s subunit of the bacterial ribosome which confers them their bactericidal property. Furthermore, they also show some anti-inflammatory properties, but the exact mechanism of action through which they modulate inflammation is poorly understood [9,16,106]. Erythromycin and azithromycin are effective in treating acne [107] but should only be used when other antibiotics are not tolerated or when tetracyclines have failed because of increasing antibiotic resistance [9,16,106]. Azithromycin has a long half-life of 68 h, which allows for a dosing regimen of 3 times a week for 4–5 weeks in acne patients [9,16,106,107]. This less-frequent dosage regimen could positively impact adherence to treatment in some patients [106]. Amoxicillin is a beta-lactam antibiotic that has some data, albeit limited, on its benefits for acne. In vitro, amoxicillin is as effective as minocycline in inhibiting *C. acnes* growth [108]. A small, retrospective review found that amoxicillin was effective in improving acne severity when combined with topical and hormonal treatments in patients who had a previous history of not responding to systemic antibiotics [109]. The recommended amoxicillin

dose for adult patients with acne is 250–500 mg 3 times a day for 4–6 weeks [9,16,106]. Furthermore, amoxicillin has a pregnancy category B classification, so despite the lack of controlled trials, amoxicillin could be a safe and effective alternative to tetracyclines in pregnant patients [9,16,106]. Trimethoprim-sulfamethoxazole (TMP-SMX), another antibiotic that could be used as an alternative to cyclines, is a bactericidal that inhibits folate production in bacteria [106]. TMP-SMX use in acne is controversial, because although it can be effective in some refractory patients, it has limited data to support its widespread use. Of note, TMP-SMZ can have potentially severe toxicities such as pancytopenia, morbilliform drug eruption, erythema multiforme, and even toxic epidermal necrolysis [9,16,106] and so should be used with caution. Therefore, current recommendations suggest that TMP-SMX should be restricted to patients who either do not tolerate tetracyclines or who are treatment resistant [9,16,106].

As with topical antibiotics, the potential for bacterial resistance and the negative impact of antibiotics on the microbiome [110] continue to present a challenge, especially when they are taken for extended periods of time [101,102,106], as is usually the case in patients with acne [111]. Current guidelines recommend limiting the use of systemic antibiotics when other alternatives are available, prescribing them for the shortest time possible (never exceeding 3 months) [2,4,9,10,15,16,18], avoiding the concomitant use of topical antibiotics [75,85] and avoiding antibiotic monotherapy [2,4,9,10,15,16,18]. Oral antibiotics, when prescribed, should be combined with a topical retinoid and benzoyl peroxide to avoid resistance [2,4,9,10,15,16,18,75,85].

3.2. Isotretinoin

Oral isotretinoin (13-cisretinoic acid) is a vitamin A derivative that is deemed by physicians to be the most clinically effective anti-acne treatment. [112] Isotretinoin was initially approved in 1982 by the U.S. FDA exclusively for the treatment of nodulocystic and conglobate acne [113], however its use has been widened to include those inflammatory cases in which other therapies have failed, those in which acne results in scarring or those with high levels of patient distress [2,4,9,10,15,16,18,114,115]. Isotretinoin is the only therapy that simultaneously targets all the pathogenic factors involved in the development of acne lesions: it decreases follicular hyperkeratinisation, inhibits sebocyte differentiation, proliferation, and lipid synthesis, modifies the inflammatory activity at the cellular level by normalizing exaggerated toll-like receptor-mediated innate immune responses, and alters the microenvironment within the duct, suppressing *C. acnes* counts more effectively than topical or oral antibiotics [112,114]. The reduction in *C. acnes* counts further contributes to the anti-inflammatory effects of isotretinoin [112].

The recommended dose goes from 0.5 to 1.0 mg/kg of body weight [2,4,9,10,15,16,18,116], which results in clearance of acne within 16 weeks in 85% of the treated patients [116]. The most common starting dose is 0.5 mg/kg/day which can be up titrated to 1 mg/kg/day based on treatment response and tolerance [116]. Lower doses of 0.1–0.5 mg/kg can be

effective and should be considered for severe inflammatory cases as they reduce the cost of treatment and also decrease side effects associated with isotretinoin therapy [117]. Low-dose intermittent isotretinoin (0.5 mg/kg/day for 1 week every 4 weeks for 6-months) is also effective and comparable to high or optimal doses [117]. However, the rate of recurrence should be considered with low-dose regimens as a systematic review found that recurrence is higher in patients who received low-dose isotretinoin when compared to patients who received the standard dose of 1 mg/kg/day (34.6% versus 21.47% respectively) although the difference was not statistically significant [117].

To observe significant improvement, a minimum of 12–16 weeks of treatment is needed; therefore, most guidelines recommend that isotretinoin should be prescribed for at least 6 months [2,4,9,10,15,16,18,116]. Once 90% of acne lesions have cleared, another 4 weeks of maintenance therapy should be prescribed to consolidate treatment before withdrawing the drug [2,4,9,10,15,16,18,116]. Importantly, approximately 6% of the treated subjects experience flare-ups of acne lesions during the early stages of treatment [117,118]; this fact should be discussed with patients during consultation. Isotretinoin usually provides a durable remission of acne; however, up to 45% of the patients may relapse after treatment and so, a second or third treatment course may be needed in about 16–29% of the patients [2,4,9,10,15,16,18]. Relapses are less frequent when treatment is continued for at least 2 months after clearance and when higher cumulative doses are achieved [116,117].

Original formulations of isotretinoin show poor water solubility [119] and need to be taken with high-fat content foods to maximize absorption [9]. Plasma levels of isotretinoin are reduced by 60% when isotretinoin is taken without food, in comparison to the levels achieved when isotretinoin is taken concomitantly with a high fat meal [120]. This has clinical implications considering that long-term acne clearance after isotretinoin treatment is dependent on the extent of systemic exposure [112,115–117] which in turn directly correlates with the amount of isotretinoin absorbed by the gastrointestinal tract over the course of therapy [119]. Patients may not be willing to regularly consume high-fat meals to optimize absorption of isotretinoin or they may be unaware of the importance of consuming a high-fat meal to improve the absorption of isotretinoin, which may in turn negatively impact efficacy of treatment and long-term remission of acne [119]. Therefore, newer formulations of isotretinoin have been developed to maximize absorption without the need of a high fat diet [119]. Lidose-isotretinoin is a form of isotretinoin that is pre-solubilized in a lipidic matrix, allowing for improved absorption even when taken with a low-fat meal [120], that received FDA approval in 2012 [112]. Pharmacokinetic studies have shown that lidose-isotretinoin is absorbed almost twice as much as conventional isotretinoin under fasting conditions (66.8% versus 39.6%) [120]. This improvement in the bioavailability of lidose-isotretinoin translates into lower rates of relapse after treatment completion when compared to treatment with the original formulations of isotretinoin [121]. In 2019, the FDA approved another formulation of isotretinoin [112,119] in which isotretinoin

was micronized and coupled with a lipid-based carrier system [119]. Due to a reduced particle size, micronized-isotretinoin shows a more consistent distribution along the intestinal tract which increases the surface area of mucosal exposure per unit mass of isotretinoin and thus improves its dissolution rate, absorption, and bioavailability [119]. A pharmacokinetic study comparing micronized-isotretinoin and lidose-isotretinoin showed that under fasting conditions, micronized-isotretinoin was absorbed at double the rate of lidose-isotretinoin, even with a 20% lower administered dose [122]. The decreased food dependency of lidose and micronized isotretinoin may improve long-term acne clearance outcomes as it facilitates systemic exposure to the drug. Furthermore, these formulations may also positively impact treatment adherence, especially in patients who exhibit irregular eating habits or those who are not comfortable consuming a high-fat content diet [119].

The most frequent clinical adverse effects during isotretinoin treatment are xeroderma, cheilitis, and blepharoconjunctivitis [112,117]. These are expected, dose-dependent [116] and can be minimized by regular use of moisturizers, lip balms, and eye lubricants [43,112,117]. Mild elevation of liver enzymes and fasting plasma lipids can be observed in all patients during isotretinoin therapy; these have little clinical relevance and tend to return to pretreatment levels rapidly after discontinuation of the drug [112,117]. Some authors consider, therefore, that routine screening tests during treatment are not worthwhile [123], while others recommend monitoring of plasma liver enzymes and lipids before treatment, 1 month after starting treatment and every 3 months thereafter [124]. A dose reduction or total discontinuation is warranted if serum transaminase or serum lipids are persistently raised [124].

The use of isotretinoin can be challenging in females because of its severe teratogenicity [112,117], and so isotretinoin should only be prescribed to women of childbearing age under strict pregnancy prevention measures [9,16,18,114]. These include the use of two different contraceptive methods of which one of them should be a barrier method, for at least 1 month before starting treatment and for at least 1 month after discontinuing treatment [9,16]. Furthermore, female patients should present with a negative serum pregnancy test result within 3 days before initiating treatment and before each monthly prescription [9,16,18].

The association between isotretinoin and psychiatric disturbances, such as depression and suicidal behavior, remains an area of uncertainty [10]. Most guidelines and expert panels agree that there is not enough data to support that isotretinoin increases the risk of psychiatric symptoms [9,10,16,18]. A Cochrane review found no difference in the frequency of depression or suicide between oral isotretinoin and other oral or topical acne treatments [125]. A retrospective study that analyzed the psychiatric adverse events reported to the FDA from 1997 to 2017 found that suicide rates among patients on isotretinoin therapy were lower than the national average [126]. This study also reported that the most common psychiatric manifestations found in patients taking isotretinoin were depression (42.3%), emotional lability (16.3%), and anxiety (13.5%), but it is unclear if they were a result of isotretinoin

therapy [126]. The overall relative risk of adverse neuropsychiatric adverse effects between isotretinoin-exposed and unexposed group is estimated at 0.88 (95% confidence interval 0.77–1.00) [127]. Furthermore, there is some data that suggests that the use of isotretinoin improves psychiatric well-being in patients with acne. Two systematic review and meta-analysis on the risk of depression in patients taking isotretinoin reported that isotretinoin use does not appear to be associated with an increased risk of depression [128] and that in fact it improved depression symptoms in patients with acne [128,129]. However, there is also evidence that strongly supports a link between isotretinoin and psychopathology [130], therefore some acne treatment guidelines propose that the patient's medical history on previous symptoms of depression should be assessed [2,4,9,10] and the possible risk of psychiatric symptoms should be discussed with the patient and their family before initiating treatment [10,18]. Furthermore, any mood or behavioral changes, depression, anxiety, and/or suicidal ideation should be monitored by the patient, their family and the treating physician during treatment with isotretinoin [9,16,18]. When present, psychiatric symptoms usually resolve rapidly (within days or weeks) after discontinuing the drug [127]. A potential link between isotretinoin and sexual dysfunction has also been reported, however the evidence currently available supporting this claim is weak, mainly because of the lack of a standardized definition of what 'sexual dysfunction' encompasses. A recent comprehensive scoping review on sexual dysfunction and isotretinoin use found that more than half the studies included reported a beneficial or neutral effect of isotretinoin on sexual function [131], however, randomized placebo-controlled trials are needed in order to determine the impact of isotretinoin therapy on sexual health so that more substantial recommendations can be made.

Alternatives to isotretinoin include a systemic antibiotic plus a topical-fixed combination (topical retinoid/BPO) [2,4,9,10,16]. A multicenter, randomized, controlled, investigator-blinded study that compared the efficacy and safety of oral isotretinoin versus doxycycline 200 mg plus adapalene 0.1%/BPO 2.5% gel in 266 subjects with severe nodular acne over the course of 20 weeks found that doxycycline plus adapalene/BPO has an earlier onset of action in reducing nodules, papules, and pustules as well as total lesion count when compared to isotretinoin at week 2. Furthermore, subjects treated with doxycycline plus adapalene/BPO showed less treatment-related adverse events when compared to patients treated with isotretinoin. However, isotretinoin was superior in reducing nodules, papules, pustules, and total lesion count at week 20. The study also found that doxycycline plus adapalene/BPO was non-inferior to isotretinoin in the intent-to-treat population ($p=0.13$, confidence interval 95%). This study, therefore, concluded that doxycycline plus adapalene/BPO has a favorable efficacy/safety profile when compared to isotretinoin, and that doxycycline plus adapalene/BPO is an adequate alternative to isotretinoin in patients who are unwilling or unable to take isotretinoin to treat their severe acne [132]. A Cochrane review also found no clear evidence to suggest that isotretinoin is superior to standard oral antibiotic/topical combination treatment in decreasing total inflammatory

lesion count, although it does slightly improve physician-assessed acne severity [125]. Furthermore, doxycycline plus adapalene/BPO is more cost-effective than isotretinoin over the course of treatment [133], which could potentially improve adherence in patients who need to pay out-of-pocket for their medication. Alternatively, oral antibiotic plus azelaic acid can also be used [10,16], especially in cases where topical retinoids cannot be prescribed, such as in pregnant patients. In non-pregnant females, an oral anti-androgenic hormonal agent [9,10,16], such as combined oral contraceptives or spironolactone [9,16], can also be added to a topical fixed combination as an alternative to oral isotretinoin therapy.

4. Maintenance therapy

Acne frequently follows a chronic remitting course [2,4,9,10,15,16,18]. Most patients experience a marked improvement with the initial treatment that is followed by severe relapses, sudden flares, or gradual re-occurrences [4] once the treatment is stopped [16]. Therefore, maintenance treatment should be prescribed once the patient is clear or almost clear of acne lesions, and clinical improvement has been achieved [2,4,9,10,15,16,18]. To avoid recurrences and relapses, maintenance treatment should target the formation of the microcomedo [2,4,16]. Therefore, topical retinoids are the gold-standard for maintenance [2,4,9,10,15,16,18]. Furthermore, topical retinoids also improve the development of secondary lesions, such as hyperpigmentation and scars [30–32], making them the preferred topical choice for treating these sequelae [31,32]. Azelaic acid [4,9,10,16,63] can also be used as an alternative to topical retinoids as it appears to have similar efficacy to adapalene during maintenance treatment [63]. Furthermore, azelaic acid also improves post-inflammatory hyperpigmentation [64]. Benzoyl peroxide can also be added to treatment in patients recovering from inflammatory acne [9,10,16]; nevertheless, it should not be used as monotherapy for maintenance due to its lack of effect on microcomedos [16]. Topical or oral antibiotic monotherapy is not recommended for maintenance, not only because they increase antibiotic-resistant *C. acnes* but also because they do not prevent the development of microcomedos [75].

5. Conclusions

Early diagnosis and treatment of acne vulgaris is imperative [15], because although acne tends to resolve naturally over the years [8] it can cause long-lasting side effects, such as permanent facial scarring, hyperpigmentation [1,2,4,9,10], and serious psychological afflictions [11,12], burdening those afflicted by the disease [12,13] and causing a negative impact on their quality of life [11,12]. Effective treatment involves the use of therapies that target most of the pathogenic factors attributed to the development of acne lesions as possible, and so, therapeutic strategies are centered on a systematic treatment escalation based on disease severity, extent, and treatment response; starting with topical treatment plans for mild-to-moderate cases and progressing over to systemic therapies in more severe cases [1,2,4,9,10,15–18]. Correctly identifying the predominant type of lesion and the extent of the disease

helps the clinicians decide on the type of treatment warranted [4,15].

Topical retinoids should be the base of treatment in most acne patients [2,4,9,10,15,16,18] as they have comedolytic, anti-comedogenic [31–33], and anti-inflammatory properties [31,32]. Thus, monotherapy with a topical retinoid should be used as first-line treatment for acne that exclusively presents with comedos [2,4,9,10,15,16,18]. As acne becomes more inflammatory, with the presence of papules and pustules, adding an antimicrobial agent should be considered [2,4,9,10,15,16,18]. The choice of antimicrobial will largely depend on the severity of the papulopustular acne [2,4,9,10,15,16,18]. Topical antimicrobials such as BPO or topical antibiotics are preferred for mild-to-moderate papulopustular acne, while oral antibiotics are warranted in moderate-to-severe cases [2,4,9,10,40,75]. Nodular and/or conglobate cases should preferably be treated with oral isotretinoin [2,4,9,10,15,16,18].

After successful induction therapy, maintenance treatment should be initiated to avoid recurrences and relapses [2,4,9,10,15,16,18]. Topical retinoids are the treatment of choice for maintenance therapy [2,4,9,10,15,16,18]. Benzoyl peroxide can also be added to treatment in patients recovering from inflammatory acne [9,10]. In fact, BPO is currently the topical antimicrobial of choice for maintenance treatment as it has similar efficacy to topical antibiotics in treating acne [47] without inducing microbial resistance in the long run [47,50]. Alternately, azelaic acid can also be used in maintenance [10,63].

6. Expert opinion

As a chronic inflammatory disease, acne vulgaris often requires prolonged treatment courses. Successful acne management requires, therefore, therapies that are not only effective but also well tolerated for longer periods of time. The ideal acne treatment would simultaneously and safely target all of the pathogenic factors implicated in the development of inflammatory and non-inflammatory lesions with minimal side effects. Although isotretinoin does target all of the pathogenic factors involved in the development of acne lesions, it is associated with potential severe side effects and should be used with caution in women of child-bearing age because of its severe teratogenicity [112,114]. There is an urgent need for a blockbuster drug that targets all of the pathogenic mechanisms involved in acne lesions to simplify treatment without skin irritation and systemic side effects. However, until this drug is developed, combination therapy that target as many pathogenic factors as possible will still be the foundation of treatment for most acne patients.

When choosing the most appropriate therapy for the patient, the clinician should evaluate the severity and extent of the disease. This in itself may pose a challenge for physicians due to the discrepant use of classification systems across treatment guidelines and expert consensus, making it difficult to draw clear and succinct conclusions about the recommendations given across the published literature. Therefore, a universally accepted common classification would be helpful in unifying the current inconsistent recommendations available. Other important factors to consider when deciding on

a treatment regimen are skin phototype, individual skin reactivity, patient compliance, effect of disease on quality of life, individual patient treatment preferences, patient understanding about acne and the therapy selected, environmental factors as well as local prescribing regulations, reimbursement systems, and insurance practices [15] as they may impact adherence.

Expert groups and evidence-based guidelines agree that for all severities of acne (except in nodular, cystic, or conglobate cases where the use of isotretinoin is warranted), topical retinoids should be considered the foundation of acne therapy as successful, long-term acne management requires that hyperkeratinization of the infundibulum and excessive sebum production be targeted to clear comedos and avoid microcomedo formation. Clinical data from many thousands of patients show that topical retinoids are highly efficacious in treating both noninflammatory and inflammatory acne lesions, and so, most acne patients will benefit from the use of a topical retinoid during active treatment and during maintenance therapy.

Before retinoids became available for the treatment of acne in 1972 [134], antibiotics had been the mainstay of treatment for years. In 2021, dermatologists prescribed more oral antibiotics per clinician than all other specialties, with the majority of antibiotics used for acne treatment [135]. Although antibiotics may improve acne symptoms in some patients, they do not reliably resolve the condition because acne is not a traditional infectious disease; it is rather an inflammatory disorder. Of note, antibiotics in acne are usually prescribed for months, rather than for days in traditional infections [75]. This exerts a considerable amount of selective pressure on pathogenic and non-pathogenic organisms, leading to resistance and dysbiosis [87,110]. Interestingly, resistance during acne therapy not only occurs in treated individuals, but can also affect their close household contacts [32]. Thus, bacterial resistance and dysbiosis prevention should be one of the essential considerations when selecting antimicrobial therapy for acne. Antibiotic therapy should, therefore, be avoided when effective alternatives are available. Previous to March 2024, the use of BPO instead of topical antibiotics was considered an adequate alternative, as its effectiveness is comparable to topical antibiotics without the associated bacterial resistance [47,49]. However, the newest evidence on the presence of benzene in BPO products should be now considered. More data is needed to determine the long-term safety of BPO products and to be able to provide evidence-based recommendations. In the meantime, however, patients should perhaps be advised to keep their BPO refrigerated to limit heat-induced decomposition and to renew their medication every 3–6 months [58]. Furthermore, reformulation of BPO products with special attention to benzene formation and stability of BPO should be undertaken by the industry. New bactericidal therapies that offer a more tolerable experience than BPO for controlling *C. acne* population and biofilm growth formation without the risk of antibiotic resistance are also being developed and evaluated for use in acne patients. These include nitric oxide releasing agents [136,137], antimicrobial cationic peptides [138–141], modified-diallyl disulfide oxide [142] and biofilm matrix degradation gels [143]. In the future, these

antimicrobials could potentially substitute the use of antibiotics in acne altogether.

Combination therapies should be used in the majority of patients with acne, as they are more effective and are usually better tolerated than their individual monotherapies. Nevertheless, the impact that multiple combination therapies have on a patient's adherence to treatment must also be considered because adherence tends to improve if the regimen is simplified and if only one treatment is prescribed [144]. Therefore, fixed-dose combination products should be considered for most patients as they are more convenient, easier to use and can be more cost-effective than prescribing different formulations separately.

One of the newest additions to acne's treatment arsenal is clascoterone, the first topical anti-androgen that targets sebum production and that can be safely used in both male and female patients due to its low systemic absorption. Clascoterone has proven to be more effective than vehicle in improving non-inflammatory and inflammatory acne lesions [91,94,145]; however, further studies on the long-term safety and efficacy of clascoterone in combination with other therapies are warranted to better determine its clinical usefulness in specific patient populations. Furthermore, access and maintenance of treatment with clascoterone could be impacted by its current high cost [16] and should be considered when prescribing a treatment.

It is also important to consider the use of cleansers, moisturizers, and dermocosmetics in acne patients, as they can play a role in the prevention, treatment, and maintenance of acne vulgaris [42] and can improve the efficacy and tolerability of acne treatments [42,43]. Cleansers and moisturizers may prevent the appearance of new acne lesions and reduce inflammation by improving skin barrier integrity and function [66]. Maintaining an intact skin barrier is of utmost importance during acne treatment to improve outcomes [42,43]. Cleansers and moisturizers not only support epidermal barrier repair in acne-affected skin [43,43,146], but they also normalize the skin's surface pH, which reduces inflammation, thereby preventing epidermal hyperproliferation [146,147]. Some studies have demonstrated that the use of a cleanser and a moisturizer in patients with mild acne, reduced acne, improved dry skin and increased levels of endogenous ceramides [148]. Although there is a lack of guidelines available regarding the role of cleansers and moisturizers in acne patients, expert panels have suggested that these types of dermocosmetics offer the ability to better tolerate topical acne treatments [42,149] and should therefore be considered in all patients with acne. Some actives present in topical dermocosmetic formulations, such as vitamin C and niacinamide, have been shown to have sebo-suppressive and antioxidant effects studies [66] which could also positively impact on the improvement of acne and therefore could be added to standard acne treatment.

Furthermore, all acne patients should be advised to avoid or minimize exposure to ultraviolet light (natural and artificial) by using adequate sun-protection (hats, sunblock, and protective clothing), especially when using topical retinoids, benzoyl peroxide, oral antibiotics, or isotretinoin as they can cause photosensitivity [112] particularly when compliance with these sun-

protective measures are lacking. Last but not least, an adequate doctor-patient relationship is of utmost importance. Since acne frequently follows a relapsing and remitting course, good communication is paramount to help the patient navigate the expected relapses.

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