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An overview of treatment options for mild-to-moderate acne based on American Academy of Dermatology, European Academy of Dermatology and Venereology, and Italian Society of Dermatology and Venereology guidelines

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Abstract

Acne is a common inflammatory skin disorder affecting the pilosebaceous unit. Patients with mild-to-moderate acne can be treated with a combination of topical, systemic, and physical therapeutic approaches, with different results depending on patient, disease, and treatment characteristics. Herein we describe and discuss the common and alternative treatment options used for mild-to-moderate acne, by comparing three widely distributed guidelines (American Academy of Dermatology, European Academy of Dermatology and Venereology, and Italian Society of Dermatology and Venereology.

KEYWORDS

acne, acne mild-to-moderate, acne vulgaris, antibiotics, guidelines, retinoids, therapy

1 | INTRODUCTION

Acne is a chronic inflammatory disease of the skin, affecting the pilosebaceous unit.[1] It has a multifactorial pathogenesis, with a typical onset in the puberal phase and a male prevalence. In adolescents the incidence of this condition might reach 87%,[2] although it is also found in adulthood, with a female prevalence.[3] A state of hyperseborrhea, together with follicular obstruction, inflammation, and infection by the *Propionebacterium acnes* contribute to the pathogenesis of the disease. In recent years, a great number of studies have investigated mild-to-moderate acne and a flourishing production of clinical trials led to new management strategies for acne, with both pharmacologic and non-pharmacologic approaches. Those studies underlined the importance of early diagnosis and prompt treatment, and this narrative review intends to summarize the most important and relevant data on mild-to-moderate acne.

The characteristics of the lesions are closely related to the various stages of the disease.[1] Typical lesions are comedones, small papules centered by a white point (close comedones) or by a black point (opened comedones), indicative of a dilatation of the follicular opening such as to allow the oxidation of the lipid content that clinically will appear black (mild acne). The initial lesions may worsen, with inflamed papules and pustules (moderate acne) and inflamed cystic nodules (severe acne). These lesions occur in areas with higher density of sebaceous glands: frontal region, nose-genien, chin, and upper back; they typically occur at puberty, when hormonal production stimulates these glands and may persist until adulthood.

2 | TREATMENT OF MILD-TO-MODERATE ACNE

By comparing the guidelines of the American Academy of Dermatology (AAD),[4] European Academy of Dermatology and Venereology (EADV),[5] and Italian Society of Dermatology and Venereology (SIDeMaST),[6] it appears a general concordance in the choice of products to be used (Tables 1 and 2); however, some details need to be further investigated.

TABLE 1 Treatment options for mild-to-moderate acne according to different guidelines

Acne	AAD[4]	EADV[5]	SIDeMaST[6]
Mild comedonal Mild papulopustular Moderate papulopustular Moderate nodular	No differentiation between comedonal and papulopustular *First line:* BPO or topical retinoid or topical combination therapy[a] BPO + topical retinoid or BPO+ topical antibiotic or BPO + topical retinoid + topical antibiotic *Alternative treatment:* add topical retinoid or BPO (if not on already) or consider alternate retinoid or topical dapsone No differentiation between papulopustular and nodular *First line:* topical combination therapy[a] BPO + topical antibiotic or BPO + retinoid or BPO + retinoid + topical antibiotic- or -systemic antibiotic + topical retinoid + BPO- or -systemic antibiotic + topical retinoid + BPO + topical antibiotic *Alternative treatment:* consider alternate combination therapy or consider other systemic antibiotic or consider systemic isotretinoin FEMALE OPTIONS: Add oral contraceptive or oral spironolactone to first line options	*High strength of recommendation:* *Medium strength of recommendation*: topical retinoid *Low strength of recommendation:* azelaic acid or BPO *High strength of recommendation:* adapalene + BPO (f.c.) or BPO + clindamycin (f.c.) *Medium strength of recommendation:* azelaic acid or BPO or topical retinoid or topical clindamycin + tretinoin (f.c.) or systemic antibiotic + adapalene *Low strength of recommendation:* blue light or oral zinc or systemic antibiotic + azelaic acid or systemic antibiotic + adapalene + BPO (f.c.) or systemic antibiotic + BPO or topical erythromicin + isotretinoin (f.c.) or topical erythromicin + tretinoin (f.c.) *High strength of recommendation:* systemic isotretinoin *Medium strength of recommendation:* systemic antibiotic + adapalene or systemic antibiotic + azelaic acid or systemic antibiotic + adapalene + BPO *Low strength of recommendation:* systemic antibiotic + BPO FEMALE OPTIONS: Hormonal antiandrogens + systemic antibiotic + topicals (apart from antibiotics) or hormonal antiandrogens + topical treatment (apart from antibiotics)	*High strength of recommendation*: *Medium strength of recommendation:* topical retinoid *Low strength of recommendation*: azelaic acid or BPO *High strength of recommendation:* BPO + adapalene (f.c.) or BPO + clindamicin (f.c.) *Medium strength of recommendation:* BPO or topical retinoid or azelaic acid or systemic antibiotic + adapalene *Low strength of recommendation:* topical erythromicin + tretinoin (f.c.) or topical erythromicin + isotretinoin (f.c.) or systemic antibiotic + BPO (f.c.) or systemic antibiotic + azelaic acid (f.c.) *High strength of recommendation:* systemic isotretinoin *Medium strength of recommendation:* systemic antibiotic + adapalene or systemic antibiotic + azelaic acid *Low strength of recommendation:* systemic antibiotic + BPO FEMALE OPTIONS: Hormonal antiandrogens + topicals or oral antiandrogens + systemic antibiotics

Abbreviations: AAD, American Academy of Dermatology; BPO, benzoyl peroxide; EADV, European Academy of Dermatology and Venereology; f.c., fixed combination; SIDeMaST, Italian Society of Dermatology and Venereology.
[a]Drugs that can be prescribed as fixed combination or as separate component.

In mild acne, EADV and SIDeMaST guidelines differentiate the comedonic type from the papulopustular one, while the American guidelines do not endorse this differentiation.[4-6]

In the comedonic form, the treatment of choice is topical retinoid, while in the papulopustular forms the treatment of choice is the combination of topical therapy, based on retinoids, benzoyl peroxide (BPO), and antibiotic therapy followed, in second line, by a topical and systemic antibiotic combination.[5,6] Also for the treatment of moderate acne there is an additional subdivision by EADV and SIDeMaST, defining the moderate papulopustular form and moderate nodular acne.[5,6]

In case of papulopustular acne the first-line treatment is a combination of topical therapies. While there is medium strength of recommendation for topical drugs plus systemic antibiotics.[5,6]

In case of moderate nodular acne, EADV and SIDeMaST guidelines propose oral retinoids as a first choice of treatment, which is instead proposed as an alternative to first line treatment by AAD.[4-6]

In all the guidelines then, there is particular attention to female subjects, where it is proposed, in cases of moderate acne, the addition of oral antiandrogens, which, in the case of EADV and SIDeMaST, is specifically reported in the context of moderate nodular acne.[4-6]

2.1 | Retinoids

Retinoids are derivatives of vitamin A, used as treatment in various skin conditions. This is related to their multiple effects on cell proliferation and differentiation, particularly on the keratinization process and inflammation. Their role in the treatment of acne is due to the presence on the sebocyte of nuclear receptors for retinoids type A, X (RAR, RXR).[7] Bonds with acid ligands to trans retinoic and 9-*cis* retinoic leads to heterodimer activation, binding of the compound to the DNA-promoting region and consequent action on the transcription of related genes.

TABLE 2 Results and side effects of commonly used compounds for the treatment of acne

Drug	Results	Side effects
Topical retinoids (adapalene, tazarotene, tretinoin)	• reduction of inflammation • regulation of keratinization • reduction of post-inflammatory pigmentation	• erythema • dryness • skin exfoliation
Topical dapsone	• anti-inflammatory action	• dryness • erythema • exfoliation • pruritus • methemoglobinemia
Peroxide benzoyl	• anti-inflammatory action • mild comedolytic effect	• erythema • dryness • discoloration of fabrics
Topical antibiotics (clindamycin, erythromycin)	• antibacterial activity • anti-inflammatory action	• drug resistance • erythema

Retinoids are classified into three generations, according to molecular structure; first generation retinoids are nonaromatic including isotretinoin (13-*cis* retinoic acid), tretinoin (all-*trans* retinoic acid), and alitretinoin (9-*cis* retinoic acid).[7] Those of second generation are monoaromatic compounds, such as etretinate and its metabolite acitretin. They are more lipophilic than those of first generation. The third-generation group includes polyaromatic compounds, such as adapalene, tazarotene, and bexarotene.

The most used retinoids in the therapy of acne are isotreninoin, adapalene, and tazarotene. There is general agreement in the use of these compounds early in mild acne; this because, in the phase of comedonic acne, characterized by follicular obstruction due to a keratinocyte plug, they regulate the keratinization process.

They are also used in case of papulopustular lesions, as they act on the inflammatory process and on the lipogenesis itself.[7]

Specifically, AAD, EADV, and SIDeMaST agree in the use of topical retinoids as first line treatment, alone or combined, in mild and moderate acne, reserving the use of oral isotretinoin as a second line for papulopustular and nodular lesions resistant to topical treatment.[4-6]

The effectiveness of topical retinoids was evaluated in a recent review including a total of 54 scientific papers, that assessed both retinoids as monotherapy and combined as well as comparisons between different topical retinoids.[8] Analysis of these studies showed that the use of topical retinoids is effective and increases in a dose-dependent manner: there are formulations with different concentrations of topical retinoids (adapalene gel may be used in 0.1% or 0.3% formulations), as well as combination with other topical antimicrobial agents (BPO, clindamycin, salicylic acid); the latter combination seems to be more effective than monotherapy.[8]

Furthermore, the use of the topical association BPO/retinoid in place of the antibiotic appears to be better to prevent the risk of resistance. Comparative analysis of various studies showed that, in the case of mild acne, any of the topical retinoids could be used, whereas in more severe forms the combination with topical antimicrobials and/or oral antibiotics was more effective.[8] Moreover, tretinoin was faster in resolving inflammation than tazarotene. In addition, tolerability and safety were also acceptable, with dryness, irritation, and erythema as major side effects; among different topical retinoids, adapalene seems to be more tolerated than tazarotene and tretinoin.[8]

2.2 | Peroxide benzoyl

BPO is a topical agent used in the treatment of mild and moderate acne.[4-6] It has a bactericidal activity against *P acnes*, thanks to its ability, once penetrated into the skin, to produce free radicals that oxidize bacterial proteins.[9] It also possesses some keratolytic and sebum-regulating. It exists in different formulations (2%, 5%, 10%) as well as in different solutions and it is the treatment of choice, alone or in combination, in mild and moderate acne therapy. In fact, to date no resistance has been found by the pathogen.[9] Again, several clinical studies have shown the greatest effectiveness when used in combination with topical retinoids or topical antibiotics. As major side effect it gives irritation and erythema; moreover, it can discolor clothes.[9]

An important problem concerns the formulation of the topical product. In fact, when crossing the layers of the epidermis, the drug risks losing its effectiveness and increasing the side effects.

For this reason, new formulations have been designed; some of them provide preparations of BPO to 4% and 8% in a base of hydrophase, in the form of cream to rinse and gel; this formulation reduces irritation.[10,11]

A multicenter study evaluated the efficacy of BPO 4% cream in hydrophase base for 6 weeks.[11] Results showed a satisfactory response, with good efficacy (85.6%) and reduced irritation.[11] In addition, a recent study attempted to incorporate the nanocrystals of BPO into an adapalene-loaded microparticulate lipid matrix[12]; this formulation promotes the deposition of the product into the follicle, favors microbicide effects and increases the effectiveness of the adapalene; reducing contact with the stratum corneum, it reduces irritation, which is a frequent side effect.[12]

2.3 | Dapsone

Dapsone is an antibacterial from the sulphon family.[13] Initially approved at 5% in topical formulation, it requires a double daily application, which can make the patient less compliant to therapy. It has anti-inflammatory action by inhibiting neutrophil chemotaxis and limiting damage induced by free radicals.[1,13] It was formulated with a higher percentage, 7.5% in a single daily dose, in the treatment of acne in patients over 12 years of age.[13] This posology minimizes systemic exposure of the drug, which is 25% to 40% lower than the 5%

formulation. Two pilot studies comparing the application of dapsone to 7.5% once daily vs vehicle were performed to assess the efficacy, safety, and tolerability profile in patient >12 years of age.[13] Studies showed that, 12 weeks after initiation of treatment, there was a reduction in noninflammatory and inflammatory lesions. The response to dapsone was also rapid, with results on inflammatory lesions visible as early as 2 weeks.[13] As for the tolerability profile, it was relatively similar in the two groups, with more reactions in the dapsone group than in the vehicle and were mainly related to the application site and reported as mild. Comparative studies of dapsone at 5% and 7.5% showed no significant differences in tolerability and side effects (irritation, dryness).[13] Among the adverse effects due to topical dapsone, methaemoglobinaemia is a serious yet rare complication that should be promptly diagnosed. AAD recommend the use of dapsone in the treatment of mild and moderate acne, alone or in combination with retinoids, at a dose of 5% to be applied twice daily, while EADV and SIDeMaST do not support its use.[4-6]

2.4 | Antibiotics

Several factors are involved in the pathogenesis of acne, including the infection by *P acnes* which, through its products, is able to induce and amplify the inflammatory process. The pathogen is able to amplify the inflammatory response acting through Toll-like receptors (TLR) activation, upregulation of metalloproteinase, and induction of proinflammatory cytokines.[14] The use of antibiotics is intended to act against the bacterium and, consequently, to reduce the inflammatory process. In the guidelines of mild-to-moderate acne, topical antibiotic treatments, predominantly based on 1% clindamycin, are considered at the forefront.[4-6] Several clinical studies have shown that combined therapy (with retinoid or BPO) is more effective than monotherapy with the antibiotic.

In particular, a recent Japanese randomized multicenter study assessed the efficacy of the fixed combination of 1.2% clindamyc.[15] After 2 weeks of treatment, although both groups experienced clinical improvement, the fixed combination had been more effective in the reduction of total lesions ($P = .008$) compared to adapalene/clindamycin combination. This significant difference was also evident in the reduction of inflammatory lesions ($P < .05$).[15]

Another topical option is the use of 2% erythromycin but is less effective than clindamycin due to resistant strains.[4] In this regard, an American retrospective study assessed the trend of acne treatment over a period of 20 years, finding a reduction in the prescription of topical erythromycin ($P < .001$) and an increase in the use of clindamycin ($P < .05$).[16]

Considering the molecular structure and effectiveness, tetracyclines (minocycline, doxycycline, and erythromycin) are preferred. The use of combination of BPO + retinoids has had a major impact on the use of antibiotics, as the potent bactericidal action of BPO has allowed to limit the use of antibiotic and, as a result, induction of drug resistance.

However, the problem of antibiotic resistance is a daunting issue and its importance (clinical and economical) is being recently investigated. In a 10-year UK study, an increase in antibiotic resistance was found in more than 50% of acne patients treated with antibiotics.[17] This problem is worldwide, reaching 91% of the combined *P acnes* resistance to erythromycin and clindamycin.[18,19] As an attempt to overcome the obstacle of antibiotic resistance, in addition to the alternatives listed above, such as the choice of combined therapies, a 2018 work assessed the effectiveness of the molecule VCD-004 against *P acnes*.[18] It is able to act against resistant strains, reducing the production of proinflammatory cytokines. It is also able to interfere with the accumulation of NF-kB induced by the bacterium. Given its capabilities, this molecule appears to be of potential use in topical acne therapy.[20]

2.5 | Alternative treatments

2.5.1 | Herbal extracts

Plants have always been used in the medical field, exploiting their natural capacities. They have been considered also in acne therapy because of their antibacterial action, thus trying to limit the use of antibiotics.

A single center RCT evaluated the effectiveness of a propolis, tea tree oil, and *Aloe vera* cream (PTAC) vs 3% topical erythromycin and vehicle (ERC) in the treatment of 60 patients with mild-to-moderate acne[21]; patients were evaluated at baseline and 15 and 30 days after initiation of treatment. Results showed reduced erythema or papular and scar lesions: specifically, the PTAC formulation was better than ERC in reducing erythema scars ($P = .003$), acne severity index ($P = .0368$), and total lesion count ($P = .001$) after 30 days.[21]

A clinical study in 71 patients with moderate and mild acne compared the application of herbal extracts with BPO gel at 2.5% for 12 weeks.[22] Results were evaluated in terms of acne lesions, adherence to treatment, porphyrin count, and dermatology life quality index (DLQI). In both groups there was a statistically significant reduction in lesions with improvement in DLQI. However, the rate of adhesion and satisfaction was to a greater extent in the group that used herbal extracts.[22]

2.5.2 | Peeling

Chemical peel is an option that is often evaluated in combination with topical and/or oral treatments, especially for their aesthetic results resulting in reduced scarring. Chemical products used for peeling differ according to their pKa, which is the pH at which 50% of the solution is free acid.[23] There are three peeling groups: alpha hydroxyacids (citric acid, mandelic acid, lactic acid, and glycolic acid [GA]); beta hydroxyacids (salicylic acid and trichloroacetic acid), and phenol, for deep peeling.[23] The purpose of peeling treatment is to create skin exfoliation and stimulate regeneration; moreover, the inflammatory process induced by these acids leads to the stimulation of fibroblasts and the production of collagen.[24] Different chemical peels can be

used alone or combined with each other and the depth of action varies according to their different percentage, with mandelic and salicylic acid used in a superficial peeling and trichloroacetic acid (TCA) and phenol that are used to get deeper into the dermis.

Recent works have tried to compare the different peels, used alone or in combination, in the treatment of mild-to-moderate acne. A recent study evaluated the efficacy of sequential peeling with 70% GA and 20% salicylic acid (SA) as a monotherapy and in association with oral doxycycline in 45 patients with mild-to-moderate acne and the effect on serum interleukin (IL) 17 and tissue IL-1α.[25] Patients were divided into three groups, based on the sequential use of GA and SA alone (group A), sequential peeling and oral doxycycline (group B), or oral doxycycline alone (group C). Values of IL-17 and IL-1a before and after treatment were collected.[25] All three groups showed statistically significant differences in terms of lesion reduction, but did not show a statistically significant difference in responses between groups, in terms of grading before and after or counting in lesions. The only statistically significant difference was in terms of aesthetic satisfaction found in a sequential GA and SA treatment groups (P = .001). In all groups there was a decrease in IL-17 and IL-1a levels, but the latter was statistically higher in group A than in group C.[25]

Again, in the context of peeling, a previous review evaluated randomized clinical trials with a total of 387 participants. A comparative study between different types of acids commonly used in peeling was performed, including salicylic acid, TCA, mandelic acid, GA, azelaic acid, pyruvic acid, and Jessner's solution, at different percentages and also comparing peeling with other procedures, such as phototherapy, concluding that there were no statistically significant differences among those compounds, being all equally effective, with few side effects, particularly post treatment-erythema, oedema, and exfoliation.[26]

2.5.3 | Phototherapy

Several clinical studies have also evaluated the efficacy of phototherapy, using both blue light and combination of blue and red light, however, the relative high power for the reduced wavelength creates security difficulties. To try to overcome this problem a clinical study assessed the efficacy of blue light irradiation on the survival of *P acnes* with sub-milliW/cm^2 potency.[27]

Fluid and solid culture plates were then irradiated with two types of blue light wavelength, at 422 and 499 nm, demonstrating how these beams were capable of killing the bacterium in planktonic culture, while the 499 nm beam was able to reduce also the growth in solid culture medium, in the presence of oxygen. In addition, coproporphyrin III, known as a photosensitizing substance, was excited at 449 nm with low-power irradiation (milliW/cm^2).[27]

Again, in the context of phototherapies, the option of photodynamic therapy (PDT) should be mentioned. Its efficacy in the treatment of acne has been shown by several studies.[28,29] A two-center, prospective assessor-blinded, proof-of-concept study assessed the effectiveness of PDT with red light in combination with 5% gel aminolevulinic acid in the treatment of the inflammatory component of mild-to-moderate acne.[30] Thirty-five patients with moderate acne were enrolled and clinical status was assessed considering Global Acne Grade System (GAG) at baseline and after three sessions of PDT (each of 15 minutes) with a statistically significant reduction of GAG score (P = .0001).[30]

2.5.4 | Laser

Lasers are often used in the treatment of scar outcomes of acne lesions.[31] However, recent studies have also highlighted the effectiveness in the active stages of the disease. Depending on the wavelength, lasers act at different levels[32,33]; in particular the infrared rays act on the sebaceous gland causing a thermal coagulation and consequently a reduced sebum production.[30] These include herbium glass and YAG laser. Other lasers that are used in acne are the diode laser and the pulse dye.[34]

A recent review assessed the use of different types of lasers and their effectiveness in acne pointing out pros and cons of each type.[34] As for erbium glass laser, several studies have evaluated the use in active acne, comparing results on inflammatory lesions and not both 1550 and 1540 nm with good clinical response and, in case of 1550 nm, also duration of efficacy. Considering YAG laser, although it is mainly used to treat scarring, it seems that 1064 nm can also be effective in active lesions, with immunohistochemical detection of inflammatory markers such as IL-8, TLR-2, and NF-kB.[34] Different is the case of YAG laser 1320 nm: it seems in fact that its effectiveness in the active lesions is weak and not lasting. As far as laser diode is concerned, the 1450 nm laser has been evaluated in active lesion studies. Treatment with this laser appears to be effective in reducing lesions and especially the duration of treatment (up to 12 months). In addition, it has also been studied on dark phototypes, IV and V, showing treatment efficacy and especially absence of long-term post-treatment hyperpigmentation. As for pulse dye laser (PDL): this laser, at 595 and 585 nm, has been shown, by various studies, to be effective in the treatment of active lesions.[34,35] It has also been evaluated in combination with peeling, resulting in more effective result than peeling alone. A RCT evaluated the efficacy and satisfaction of the use of 595-nm PDL in young patients with mild-to-moderate acne.[2] Results did not show statistically significant differences between laser-treated and untreated areas, except in papule counts.[2]

Last, KTP laser, whose mechanism of action exploits the presence of chromophores.[36,37] However, the studies performed in the pathology of acne are few and without promising results.

3 | CONCLUSION

The most effective treatment for mild-to-moderate acne is topical treatment, with BPO and retinoids, better in combination, thanks to their antibacterial, anti-inflammatory, and kerato-regulatory actions, in order to reduce the use of antibiotics, reserved for clinical resistant

cases. The main side effects are represented by erythema and dryness of the treated area, which appear to be minor for adapalene compared to tazarotene and tretinoin; new formulations have been recently proposed to overcome this problem.

In addition to traditional treatments, then, there are other therapeutic options to use both in combination and alone; peeling, for example, can be useful not only in the treatment of scarring outcomes, but also in the active phase of pathology, as well as lasers.

The choice of the best treatment option should consider the clinical extent of the disease, skin phototype, eventual skin reactivity, and also patient compliance.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

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