update on the treatment of acne vulgaris
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abstract
• objective: to provide an evidence-based review of acne treatments.
• methods: review of the literature.
• results: acne vulgaris is a chronic inflammatory condition affecting 40 to 50 million people in the united states. current treatments target at least 1 of the known pathophysiologic mechanisms involved in acne development. combination therapy with a topical retinoid and antimicrobial agent is generally recommended as first-line treatment for most patients. oral antibiotics are often used for moderate to severe acne, and their combined use with benzoyl peroxide can prevent the development of bacterial resistance. there is also good evidence to suggest that oral contraceptives containing estrogen and a progestin are effective in reducing acne lesions in women. oral isotretinoin has been shown to be effective in clearing severe nodulocystic acne and inducing remission, although it is unclear whether an association between oral isotretinoin use and suicidal behaviors exists. lasers, light sources, and photodynamic therapy are effective in the treatment of acne; however, further studies are needed to determine the appropriate duration and light source.
• conclusion: effective treatment for acne is available. patient responses vary, and often more than 1 mode of therapy may be needed.

acne vulgaris is a chronic inflammatory dermatosis of the pilosebaceous unit characterized by open or closed comedones and inflammatory papules, pustules, nodules, or cysts. it affects 40 to 50 million individuals in the united states [1], including 70% to 87% of adolescents [2]. acne is also a common skin problem in adults. Goulden et al [3] found that the prevalence of facial acne in men and women over age 25 determined by clinical examination was 3% and 12%, with 82% of cases being persistent from adolescence. More recently, Collier et al [4] assessed the prevalence of acne reported by women and men by age-group. prevalence for women and men, respectively, was 50.9% and 42.5% for ages 20 to 29 years, 35.2% and 20.1% for ages 30 to 39 years, 26.3% and 12.0% for ages 40 to 49 years, and 15.3% and 7.3% in ages 50 years and older.

Four major factors associated with the pathogenesis of acne are increased sebum production, follicular hyperkeratinization, Propionibacterium acnes proliferation, and inflammation [5].

Androgenic stimulation causes sebum production from the sebaceous glands. Excess sebum production can result from pilosebaceous unit hyperresponsiveness, increased circulating androgens, or both [5]. However, most patients do not have significant endocrine abnormalities [5].

Keratinocyte proliferation and abnormal desquamation cause follicular hyperkeratinization [5]. Keratinocytes accumulate and become densely packed with monofilaments and sebum, forming a microcomedo [5,6]. Further sebum production converts a microcomedo to a closed comedo (whitehead) when the follicular orifice is closed, or to an open comedo (blackhead) when the follicular orifice is open [5].

P. acnes is a gram-positive anaerobe that resides in the pilosebaceous unit. These bacteria attract lymphocytes, which invade and destroy the follicular wall [5]. Rupture of the follicular epithelium causes lipids, keratinocytes, and P. acnes to leak into the surrounding dermis [6]. This leads to further recruitment of inflammatory cytokines and neuropeptides, thus perpetuating the inflammatory process and resulting in inflammatory papules or nodules [6].

Several systems for grading acne exist with most involving a global assessment of the severity (eg, mild, moderate, severe) that takes into account the number, type, and extent of acne lesions [7]. Although there is no consensus on which classification system is the best, clinicians may find it useful to use a consistent system to select appropriate treatment regimens and assess responses to treatment [7].

Routine endocrinologic testing is not necessary in the majority of patients with acne [7]. However, laboratory evaluation of free testosterone, dehydroepiandrosterone sulfate, luteinizing hormone, and follicle-stimulating hormone is indicated in females presenting with signs of hyperandrogenism. Such signs can include menstrual dysfunction, hirsutism, or polycystic ovaries in adult women [5,7].

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**ACNE TREATMENT**

**Treatment for Mild Acne**

First-line therapy for mild acne involves a topical retinoid [5,6]. If an inflammatory component exists, a topical antibiotic such as clindamycin or erythromycin may be added to enhance the efficacy [5,6]. Antibiotics should not be used as monotherapy and should be discontinued when the inflammatory component is adequately treated in order to minimize the occurrence of antibiotic-resistant bacteria [5]. Topical benzoyl peroxide or azelaic acid may be added to antibiotic therapy to reduce the potential for developing *P. acnes* resistance [5].

**Topical Retinoids**

Topical retinoids should be the foundation of treatment for most patients with acne because they act to reduce obstruction of the follicle and therefore treat both comedonal and inflammatory acne [7]. They are also recommended for maintenance therapy [5]. Three topical retinoids are available in the United States: tretinoin, adapalene, and tazarotene. The number of inflammatory and noninflammatory lesions is significantly reduced by topical tretinoin [8–11], adapalene [12–14], and tazarotene [15–17].

Tretinoin was the first topical retinoid used in the treatment of acne, and adapalene and tazarotene are synthetic agents [18]. Retinoids exert their effects by binding to nuclear retinoid acid receptors (RAR) and retinoid X receptors (RXR) [18]. Cellular binding proteins (CRBP I and II) and cellular retinoic acid binding proteins (CRABP I and II) are involved in cellular transport and metabolism of retinoids [18]. Studies suggest that because adapalene activity is not dependent on CRABP II binding, it is associated with less irritation and less erythema [18]. Tretinoin may cause more adverse effects because of its involvement in several pathways, including RAR and RXR activation and CRABP II binding [18].

Tazarotene appears to be the most efficacious topical retinoid. In randomized, double-blind controlled trials and a meta-analysis, tazarotene 0.1% gel or cream was shown to be more effective than tretinoin 0.025% gel [19], tretinoin 0.1% microsphere gel [20], adapalene 0.1% gel [21], or adapalene 0.1% cream [22]. However, some randomized, evaluator-blind, controlled trials showed that tazarotene 0.1% cream was equally efficacious to adapalene 0.1% gel and 0.3% gel in total acne lesion reduction [23–25].

Adverse effects of topical retinoids include erythema, dryness, itching, and stinging. Adapalene seems to be associated with fewer adverse effects. Adapalene 0.1% gel or solution is equally effective or superior to tretinoin 0.025% gel [26,27], tretinoin microsphere 0.1% gel [28], and tretinoin 0.05% cream [29], but it is generally better tolerated and less likely to cause skin irritation [26,28–33]. Topical retinoids are available in a variety of strengths and formulations and generally should be started at a low strength to minimize potential irritation.

**Benzoyl Peroxide**

Benzoyl peroxide is bactericidal and is effective in treating acne. Benzoyl peroxide plus a topical retinoid are often used in conjunction with antibiotics to prevent or eliminate the development of antibiotic-resistant *P. acnes* [6].

In studies, patients using benzoyl peroxide 20% lotion [34], benzoyl peroxide 5% gel [35], and benzoyl peroxide 5% gel or 10% cream [36] had a significantly greater reduction of acne lesions, including both inflammatory and noninflammatory lesions, compared with controls. There appears to be no difference in efficacy among the benzoyl peroxide concentrations [37,38].

Randomized trials by Belknap [39] and Montes [40] showed that both topical tretinoin and benzoyl peroxide effectively reduced inflammatory and noninflammatory lesions. Montes [40] also concluded that benzoyl peroxide was clinically better than topical tretinoin for reducing the total number of lesions, especially comedones.

**Topical Antibiotics**

Topical antibiotics are indicated for mild inflammatory acne [6]. Both erythromycin and clindamycin are topical antibiotics that have been shown to be effective and well-tolerated. Because *P. acnes* can develop resistance to either of these antibiotics [41], their use as a single therapeutic agent is limited.

Double-blind, randomized controlled studies have demonstrated the efficacy of various topical erythromycin preparations, including erythromycin 1.5% solution and erythromycin 2% gel and ointment, in reducing inflammatory acne lesions over placebo [42–47].

Clindamycin has also been shown to be effective in the treatment of acne. In several multicenter, investigator or double-blind, randomized, placebo-controlled trials, patients using clindamycin 1% hydrochloride solution, clindamycin 1% phosphate solution, clindamycin 1% phosphate lotion, or clindamycin 1% phosphate gel had a significantly greater reduction in papule and pustule counts compared with patients receiving placebo [48–50]. Additionally, the study by Ellis et al [50] showed the clindamycin solution and gel both were associated with significant reduction of open comedones at various study intervals.

Topical clindamycin and erythromycin appear to have comparative efficacy. In double-blind and investigator-blind randomized comparisons of topical erythromycin versus topical clindamycin, both formulations showed comparative efficacy in reducing acne lesions [51–53].

An analysis of clinical trials showed that the efficacy of 1.5% to 2% topical erythromycin formulations in the treatment of inflammatory or noninflammatory acne decreased over time, especially in studies of greater than 12 weeks’ duration [54]. The efficacy of topical clindamycin remained stable throughout the study period [54].
Other Topicals

Although few well-designed trials evaluating the safety and efficacy of topical salicylic acid exist, a review of 3 placebo-controlled trials and 1 comedoytic assay concluded that salicylic acids pads reduce the number of primary lesions and acne severity [55].

Azelaic acid has comedolytic and antibacterial properties and is effective in treating acne. Several studies have shown that 20% azelaic acid is superior to placebo in reducing inflammatory and noninflammatory acne lesions or total number of acne lesions [56–58]. One study showed that 20% azelaic acid had similar efficacy compared with 0.05% tretinoin cream and another showed that although benzoyl peroxide has a more rapid effect, azelaic acid is better tolerated [57,59].

Randomized, double-blind, vehicle-controlled trials have shown that topical dapsone 5% gel is effective in reducing inflammatory and noninflammatory acne lesions and that adverse effects were comparable with those in the control group [60–62]. Use of oral dapsone may be associated with hematologic adverse effects; however, in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency treated with dapsone 5% gel, there was no clinical or laboratory evidence of drug-induced hemolytic anemia [63].

Combinations

Combination therapy is likely to have a more significant effect because it targets 3 major areas of acne pathophysiology: P. acnes proliferation, inflammation, and hyperkeratinization [5]. Topical retinoids in combination with topical or oral antimicrobials have been shown to reduce inflammatory and noninflammatory acne lesions faster and to a greater degree than antimicrobial agents alone [5]. Additionally, combination therapy is one strategy to limit the increase in resistance of P. acnes in patients [5,64].

In an 8-week study by Mills and Kligman [65], groups of patients with moderate acne who received topical erythromycin plus topical tretinoin experienced better results than those receiving monotherapy or placebo. In double-blind randomized trials, the combination topical clindamycin 1% phosphate and a topical retinoid was found to be more efficacious in reducing inflammatory acne and noninflammatory acne lesions than either agent alone [66–69]. Topical retinoids plus benzoyl peroxide have also been effective in the treatment of acne in randomized, controlled investigator- and double-blind studies [70,71].

Several double- or single-blind randomized controlled studies have demonstrated the efficacy of topical antibiotics combined with benzoyl peroxide in treating inflammatory acne [64,72–75]. Additionally, 1 double-blind randomized study by Cunliffe et al [64] demonstrated a reduction in clindamycin-resistant P. acnes counts as compared with baseline in patients treated with combination therapy, whereas P. acnes counts increased by greater than 1600% in those receiving clindamycin monotherapy.

Treatment for Moderate Acne

The use of systemic antibiotics is indicated for moderate or severe acne [5]. The most commonly used systemic antibiotics are tetracycline and its derivatives [5]. Other less commonly used antibiotics include macrolides, trimethoprim-sulfamethoxazole (TMP-SMX), and trimethoprim [5]. Like topical antibiotics, systemic antibiotics should be combined with a topical retinoid to enhance efficacy [5]. The addition of topical benzoyl peroxide reduces the development of P. acnes resistance [5]. In women, oral contraceptives containing an estrogen and progestin are indicated for moderate acne and can be used as a component of combination therapy [5,6]. For moderate nodular acne that is resistant to primary treatments, oral isotretinoin may be used [5,7].

Systemic Antibiotics

Systemic antibiotics are the standard of care for moderate and severe acne and treatment-resistant forms of acne [7]. They are generally not used as monotherapy and are ideally discontinued within 8 to 12 weeks because of the concern for increased bacterial resistance [5,7]. There is evidence to support the use of tetracycline, doxycycline, minocycline, erythromycin, TMP-SMX, trimethoprim, and azithromycin.

Oral antibiotics are also associated with a variety of side effects [7]. All antibiotics can result in vaginal candidiasis. Tetracyclines should not be used in pregnant women and children under age 8 due to deposition in bones and tooth discoloration [76]. Doxycycline is associated with photosensitivity and esophageal irritation [76]. Minocycline may cause vestibular disturbances, pigment deposition, and rarely autoimmune hepatitis or a systemic lupus erythematosus–like syndrome [77].

In double-blind randomized controlled studies, treatment with oral tetracycline was associated with significantly greater improvement in acne compared with placebo [78–84]. There are conflicting data on whether oral tetracycline is superior to topical tetracycline or whether there is no significant difference in efficacy [79–81], and it is unclear whether topical clindamycin is equally efficacious or superior to oral tetracycline [82–84].

There is insufficient evidence to support the use of 1 tetracycline over another [85,86]. A Cochrane review of minocycline in the treatment of acne concluded that there was no reliable randomized controlled trial evidence to justify the use of minocycline as first-line treatment for acne, especially considering the higher cost and concerns about more severe adverse effects [77].
A double-blind randomized controlled study by Gammon et al [87] showed that oral erythromycin and oral tetracycline were equal in efficacy in the treatment of moderate to moderately severe acne. Bacterial resistance is most common with erythromycin [88], and its use should be limited to those who cannot use tetracyclines [7].

Although oral TMP-SMX and oral trimethoprim are not recommended as first-line therapy, they have been shown to significantly reduce acne severity and can be used for acne treatment when other oral antibiotics cannot be used or patients are refractory to other oral antibiotic regimens [89–92].

An open-label, noncomparative study by Bardazzi et al [93] demonstrated a significant reduction in inflammatory lesions in patients receiving azithromycin relative to baseline.

**Oral Contraceptives**

Estrogen-containing oral contraceptives can be useful in the treatment of acne for women. In 5 randomized placebo-controlled trials, oral contraceptives reduced inflammatory and noninflammatory acne lesion counts and severity grades and improved global and patient self-assessment compared with placebo [94–98]. These trials included combinations of ethinyl estradiol plus levonorgestrel, norethindrone acetate, or norgestimate.

The comparative effectiveness of combination oral contraceptives with varying progestin components is unclear. Randomized controlled trials suggest that chloromadinone acetate–containing or cyproterone acetate–containing oral contraceptives improved acne better than those containing levonorgestrel, but the superiority is based on little evidence [99,100]. Comparisons between other oral contraceptives containing diphasic desogestrel [101–105], cyproterone acetate [101–103], levonorgestrel [104–107], drospirenone [108–112], norgestimate [108], gestodene [110–112], and norethindrone acetate [106] were either conflicting or found no differences between the combinations in the ability to reduce acne.

In a multicenter, controlled trial by Monk et al [113], no significant difference was found between low-dose cyproterone acetate and oral minocycline in the reduction of acne lesions or in the patients’ self-assessments.

Overall, good evidence suggests that combination oral contraceptives containing an estrogen and a progestin are effective for reducing acne lesions in women, even those without increased serum androgens [114]. To date, ethinyl estradiol-drospirenone, ethinyl estradiol-norethindrone acetate, and ethinyl estradiol-norgestimate are the oral contraceptives that are specifically approved by the U.S. Food and Drug Administration for the treatment of acne [115], although few differences are found between various combination oral contraceptives. There are limited data to determine the comparative effectiveness between oral contraceptives and antibiotics in reducing acne lesions.

**Spironolactone**

Spironolactone inhibits the biosynthesis of testosterone and also blocks androgen receptors [114]. This results in decreased androgen-stimulated sebocyte proliferation and a reduction in sebum excretion [114].

In randomized, placebo-controlled, double-blind studies, Muhlemann et al [116] showed that spironolactone is significantly more effective than placebo in reducing the number of inflamed acne lesions, and Goodfellow et al [117] found that patients tended to have greater improvement when taking higher doses (150–200 mg) of spironolactone. Hatwal et al [118] found that acne severity improved significantly more in participants using spironolactone compared with those using cimetidine, which has antiandrogenic effects. However, these studies had relatively small sample populations (≤50) [116–118].

Side effects of spironolactone therapy may include hyperkalemia, menstrual irregularities, breast tenderness, or hypotension [119]. A retrospective analysis by Shaw [119] showed that a lower frequency of adverse effects may be associated with lower doses of spironolactone (50–100 mg).

**Treatment of Severe Acne**

Oral isotretinoin is indicated for severe nodulocystic acne or treatment-resistant moderate acne [5]. Education of patient regarding the side effects, teratogenicity, potential psychiatric effects, and monitoring is critical in patients who are interested in initiating oral isotretinoin [5]. Alternatives to oral isotretinoin treatment include the combination of a systemic antibiotic, topical retinoid, and topical benzoyl peroxide [6]. In women, an oral contraceptive can be added to the combination [6].

**Isotretinoin**

Although oral isotretinoin is approved for the treatment of severe nodulocystic treatment-resistant acne, it is also indicated for all cases of treatment-resistant acne or acne that produces physical or psychological scarring [7]. Isotretinoin has been shown to be effective in clearing acne lesions and inducing remission. The prolonged remission may be related to continued sebaceous gland inhibition in some patients [120].

In a randomized, double-blind study by Peck et al [121], patients receiving isotretinoin had 95% improvement, which was significantly greater than those receiving placebo, who had an overall 57% increase in the number of lesions. Sixteen of the 17 patients who initially received placebo were then given isotretinoin with a 98% improvement. Twenty-seven of 32 patients cleared completely, with 18 receiving only one 4-month course of treatment. All patients were in remission at the time of the report, averaging 38 months of remission.

A double-blind study concluded that there were no significant differences in efficacy between doses of 0.1 mg/kg.
0.5 mg/kg, and 1 mg/kg, but they recommended 0.5 mg/kg as the initial dose for the initial course of isotretinoin treatment because those treated with 1 mg/kg had more severe side effects and those treated with 0.1 mg/kg had a higher incidence of relapse [122]. Similarly, another double-blind study concluded that the optimal dose-range for the treatment of patients with nodulocystic acne is 0.5 to 1.0 mg/kg because a lower dose was associated with much lower maintenance of clinical improvement [123]. In general, treatment continues until a cumulative dose of 120 to 150 mg/kg is achieved [5,7,124].

Layton et al [125] concluded that isotretinoin is safe and effective and is capable of producing long-term remission in the majority of patients in a 10-year follow-up study. Factors associated with the need for further courses of treatment included lower dosage regimens (0.1 mg/kg and 0.5 mg/kg), the presence of severe acne, females older than age 25 years, and a prolonged history of acne [126].

All patients are required to register and comply with the iPLEDGE program [7]. Isotretinoin has potential teratogenic effects, and therefore adequate contraception is necessary before, during, and 6 weeks after treatment [5]. Laboratory monitoring during therapy should include measurement of triglycerides, cholesterol, transaminases, and complete blood counts [7]. Common adverse effects of isotretinoin therapy include dry skin and eyes, secondary skin infection, myalgias, epistaxis, and decreased night vision [5].

In a multicenter, double-blind controlled study, patients with severe recalcitrant nodular acne were randomized to either micronized isotretinoin or standard isotretinoin [127,128]. Both formulations had similar clinical efficacy [127], but the micronized isotretinoin appeared to lower the risk of mucocutaneous adverse events and hypertriglyceridemia [128].

Depression and suicidal behaviors have been reported in patients taking isotretinoin [129]. However, a causal relationship has not been established. A systematic review found that rates of depression in the included studies showed similar rates of depression in antibiotic control groups, and there was no significant increase in depression after isotretinoin treatment compared with before treatment [129]. A recent case-crossover study is the first controlled study to find a statistically significant association between isotretinoin and depression [130]. Treatment of severe acne is often associated with mood improvement [7,129]; however, given the profound consequences of depression in young patients, it is prudent to advise patients on isotretinoin that the possibility of an association with depression has been raised and close monitoring is indicated [131].

Although these studies do not support a causal relationship between isotretinoin use and increased rate of depression or suicidal behavior, there may not be sufficient evidence to rule out a weak association [129]. Therefore, patients must be aware of the potential effects, and physicians should monitor for these adverse effects [7].

**Maintenance Therapy**

Topical retinoids are the preferred agent for maintenance therapy [5]. Antibiotics should be discontinued once inflammatory lesions are well-controlled [6]. If an antimicrobial agent is needed, benzoyl peroxide should be used in conjunction with a topical retinoid [6].

**Alternative Acne Treatments**

A variety of alternative acne treatments exist. While there are limited data to indicate their use as first-line therapy, these alternatives may be used in conjunction with other treatments.

**Oral corticosteroids**

There are limited data to support the effectiveness of oral corticosteroids in the treatment of acne. One study by Nader et al [132] showed that oral prednisone lowered elevated androgen levels in hyperandrogenic women with acne and was associated with clearing or significant improvement. A consensus of expert opinion supports the idea that short courses of high-dose oral corticosteroids may be of temporary benefit in patients with severe inflammatory acne [7].

**Intralesional Steroids**

Corticosteroids can be injected intralesionally in order to obtain a high concentration of steroid at the lesion site with minimal systemic absorption. In small studies, improvement has been noted in the treatment of individual acne cysts and nodules within 24 to 72 hours [133–135]. Injection of lesions may be associated with local atrophy [135], and systemic absorption may occur leading to suppression of the hypothalamic-pituitary-adrenal axis [136]. Decreasing the concentration or volume may minimize these adverse effects [7].

**Chemical Peels**

Glycolic acid is an alpha-hydroxy acid that can be used as a chemical peeling agent by inducing removal and then regeneration of the epidermis and/or dermis [137]. Salicylic acid is a keratolytic agent that has a strong comedolytic effect because of its lipophilic nature and ability to penetrate deep into pores [138]. However, there is little evidence in the peer-reviewed literature supporting the efficacy of glycolic acid–based or salicylic acid–based peeling preparations.

One randomized controlled trial compared glycolic acid and Jessner’s solution (resorcinol, salicylic acid, lactic acid, and ethanol) and demonstrated improvement in facial acne in both treatments compared with baseline [139]. There was no statistically significant difference between the treatments. Several controlled trials and case series have also
reported improvement in inflammatory and noninflammatory acne in patients using chemical peels compared with baseline [137,138,140,141].

Although chemical peels do not replace topical or systemic medications for the treatment of acne, they can be used as adjunctive therapy [142].

Comedo Removal

There is little evidence in the peer-reviewed literature regarding the efficacy of comedo removal. The extraction of comedones maybe more beneficial in superficial acne but not in cystic acne [143]. Comedo removal does not affect the course of the disease but may provide immediate improvement of the patient’s appearance [142], increase patient satisfaction [142], and positively impact compliance [7].

Complementary and Alternative Medicines

Complementary and alternative medicines are used to treat a variety of health conditions including acne. However, there are very limited data addressing the safety and efficacy of these agents.

Two clinical trials have shown that tea tree oil is an effective treatment for acne [144,145]. In double-blind, randomized, placebo-controlled clinical evaluations, certain herbal tablets have been associated with a significant reduction in the number of inflammatory and noninflammatory lesions [146,147].

In addition to causing stress and having a significant psychological impact on patients, acne may be exacerbated by stress because of an associated increased sebum excretion rate, free fatty acid production, and endocrine activity. The results of an intervention by Hughes et al [148] provided support for the efficacy of biofeedback relaxation-imagery therapy in the treatment of acne. However, the literature supporting the possible benefit of biofeedback-assisted relaxation and cognitive therapy in the treatment of acne is weak.

Lasers

Some data indicate that the use of pulsed dye lasers, potassium titanyl phosphate lasers, and infrared lasers may be of benefit in reducing acne lesions. However, data are very limited.

Two randomized controlled studies evaluated the efficacy of pulsed dye lasers versus sham treatments. Seaton et al [149] showed significant reduction of inflammatory acne lesions and total acne lesions, but Orringer et al [150] failed to show a significant difference between the laser-treated skin and untreated skin.

In a randomized controlled trial, Baugh and Kucaba [151] showed that after 4 treatments with the potassium titanyl phosphate laser, patients had significant improvement in their acne at 1 week and nonsignificant improvement at 4 weeks.

Four randomized controlled studies have evaluated the efficacy of infrared lasers for the treatment of acne. A 1320-nm Nd: YAG laser produced a significantly greater reduction of open comedones but had no difference in the reduction of papules, pustules, or closed comedones compared with no treatment [152]. A 1450-nm wavelength laser produced a significantly greater reduction in the total acne lesion count compared to the control [153]. Clinical efficacy has not been demonstrated to be enhanced with the addition of microdermabrasion to 1450-nm laser treatment [154] nor has a significant difference been shown between 2 fluencies (14 and 16 J/cm²) [155].

Light Sources

As part of its normal metabolism, P. acnes produces porphyrins, which can absorb light at the near ultraviolet and blue light spectrum [156,157]. Irradiation of P. acnes with blue light can induce photoexcitation, leading to singlet oxygen production, and eventually bacterial destruction. Several trials have studied the efficacy of various light sources and have shown some benefit.

In a randomized, evaluator-blinded study by Sigurdsson et al [158], green light and violet light significantly improved face, back, and/or chest acne, with a tendency toward violet light having better results.

Other randomized controlled trials evaluating blue light have shown its safety and efficacy in the reduction of inflammatory lesions [157,159,160] but worsening of nodulocystic lesions [160].

The randomized controlled trial by Na and Suh [161] concluded that red light alone is effective in the treatment of inflammatory and noninflammatory acne lesions, although it does not eradicate the lesions completely and effects are not sustained over the long term.

A randomized controlled study by Papageorgious et al [156] demonstrated that phototherapy with mixed blue and red light was significantly better that blue light alone, white light, and benzoyl peroxide 5% cream in improving inflammatory acne, and nonsignificantly better in improving comedonal acne.

Photodynamic Therapy

Photodynamic therapy is a therapeutic modality that utilizes a photosensitizing agent and its activating wavelength of light to selectively destroy target tissue [162]. The few randomized controlled studies that have evaluated the efficacy of photodynamic therapy have shown positive results.

Topically applied 5-aminolevulinic acid (ALA) is metabolized to protoporphyrin IX, a potent photosensitizer, that accumulates in epidermal cells and pilosebaceous units [163]. When the ALA-treated skin is irradiated with light, protoporphyrin IX is excited and reacts with oxygen to form singlet, causing membrane damage and cell destruction [163].

In a randomized controlled trials comparing photodynamic
therapy with either treatment alone or no treatment, ALA plus red light produced significantly greater reduction of inflammatory acne lesions [163,164], and ALA plus blue light produced a greater reduction in papules, pustules, and comedones [165]. Significant improvement in acne lesions was demonstrated using intense pulsed light (IPL) plus ALA and using IPL plus short-contact ALA [162,166]. Complete clearance of acne in all patients using long-pulsed dye laser (LPDL) plus ALA was shown by Alexiades-Armenakas in a controlled trial [167].

Methyl aminolevulinate (MAL) is another agent that has been studied in the photodynamic therapy of acne. It is de-esterified to ALA by intracellular enzymes [168]. Because of its lipophilicity, MAL is expected to penetrate more easily and deeper into the targeted tissue [169].

Randomized controlled trials have shown a significantly greater reduction in inflammatory acne lesions in patients treated with MAL plus red light compared with patients receiving placebo or no treatment [168,170]. In a randomized, half-face treatment study by Yeung et al [171], patients who received MAL plus IPL had a nonsignificantly greater reduction in inflammatory acne lesions compared with controls who received IPL alone or topical adapalene. The patients receiving MAL plus IPL and IPL alone had a significantly greater reduction of noninflammatory acne lesions compared with the adapalene group [171]. Haedersdal et al [172] found that the half of the face treated with MAL plus LPDL-treated had a significantly greater reduction of acne lesions compared with the side treated with LPDL-treated alone.

ALA plus red light and MAL plus red light appear to be effective in the treatment of acne with no significant differences between response rates [169].

Although several studies demonstrate the effectiveness of photodynamic therapy in the treatment of acne, further studies are needed to determine the proper incubation time of the photosensitizer and the appropriate light source.

**Conclusion**

Acne is a common condition that is often accompanied by physical and psychological morbidity. Current acne treatments target at least 1 of the known pathophysiological mechanisms involved in acne development. The Table summarizes treatment recommendations for acne. Combining these therapies can often lead to significantly better improvement and/or inhibit the development of antibiotic-resistant bacteria. With proper treatment of this condition, the negative effects of acne can be minimized.

**Table. Treatment Recommendations for Acne Vulgaris**

| Mild acne | First-line therapy is a topical retinoid Addition of a topical antibiotic/ benzoyl peroxide combination if papules/pustules present. Benzoyl peroxide without antibiotic also an option basing strength of formulation on skin dryness (oily skin higher concentration) or azelaic acid with topical antibiotic |
| Moderate acne | Topical retinoid plus systemic antibiotic Addition of a topical antibiotic/benzoyl peroxide combination or benzoyl peroxide If treatment-resistant, may consider isotretinoin |
| Severe acne | Oral isotretinoin If isotretinoin contraindicated or not tolerated, alternatives include a systemic antibiotic in combination with topicals for moderate acne |
| Adult female acne | Oral contraceptive Spironolactone Low-dose isotretinoin |
| Maintenance | Topical retinoid Benzoyl peroxide |

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