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REVIEW ARTICLE

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Current treatments of acne: Medications, lights, lasers, and a novel 650-μs 1064-nm Nd: YAG laser

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Summary

The treatment of acne, especially severe acne, remains a challenge to dermatologists. Therapies include retinoids, antibiotics, hormones, lights, lasers, and various combinations of these modalities. Acne is currently considered a chronic rather than an adolescent condition. The appropriate treatment depends on the patient and the severity of disease. The purpose of this study was to review current therapies for acne of all severities and to introduce the 650-μs 1064-nm laser for the treatment of acne.

KEYWORDS

inflammatory, infrared, *Propionibacterium acnes*, pulse duration, sebaceous, thermal relaxation time

1 | INTRODUCTION

Acne vulgaris is the most frequent reason that people consult a dermatologist.[1] Acne affects 85% to 90% of teenagers,[2] children aged 7-12 years,[3] and adult men and women, including those with skin of color.[4,5] Among adults who have acne, 64% are in their 20s and 43% are in their 30s. Prevalence is higher among women than men.[6-8]

Gollnick et al.[9] and the Global Alliance to Improve Outcomes in Acne[10] have suggested that acne be considered a chronic disease rather than a "simple, self-limiting affliction of adolescents". This assertion is based on the known characteristics of a chronic disease: an extended course, recurrence or relapse, slow onset or acute outbreaks, and negative effects on quality of life. Acne persists into adulthood in up to 50% of affected patients and has negative sequelae such as anxiety and depression, social withdrawal, scars, and persistent hyperpigmentation.[10]

2 | PATHOGENESIS OF ACNE

Acne is a multifactorial disease of the pilosebaceous unit. The development of acne lesions has been attributed to four pathogenic factors: androgen-induced overproduction of sebum, colonization of the pilosebaceous duct by *Propionibacterium acnes*, abnormal keratinization in the follicle, and discharge of inflammatory mediators into the skin.[8] The first stage is the development of a microcomedone in the pilosebaceous unit. This is a plug that forms because of increased production of sebum and keratinocytes that line the hair follicle. Accumulation of sebum and sloughed keratinocytes results in the formation of larger, visible comedones. At the same time, *P. acnes* colonizes the pilosebaceous duct, triggering the release of inflammatory mediators into the surrounding tissue and a response by immunocompetent cells, further contributing to the development of comedones.[8,11] Acne most often occurs in the face, neck, back, and chest, all areas with many pilosebaceous units.[12,13]

3 | TREATMENT OF ACNE

The traditional monotherapies for mild to moderate acne are topical retinoids and antimicrobial agents such as antibiotics and benzoyl peroxide (BPO).

3.1 | Retinoids

Members of the Global Alliance[10] state that retinoids should be considered the basis for treatment of all acne patients except those with the most severe disease. Topical retinoids (e.g, tretinoin, tazarotene, adapalene) help to normalize the abnormal differentiation and

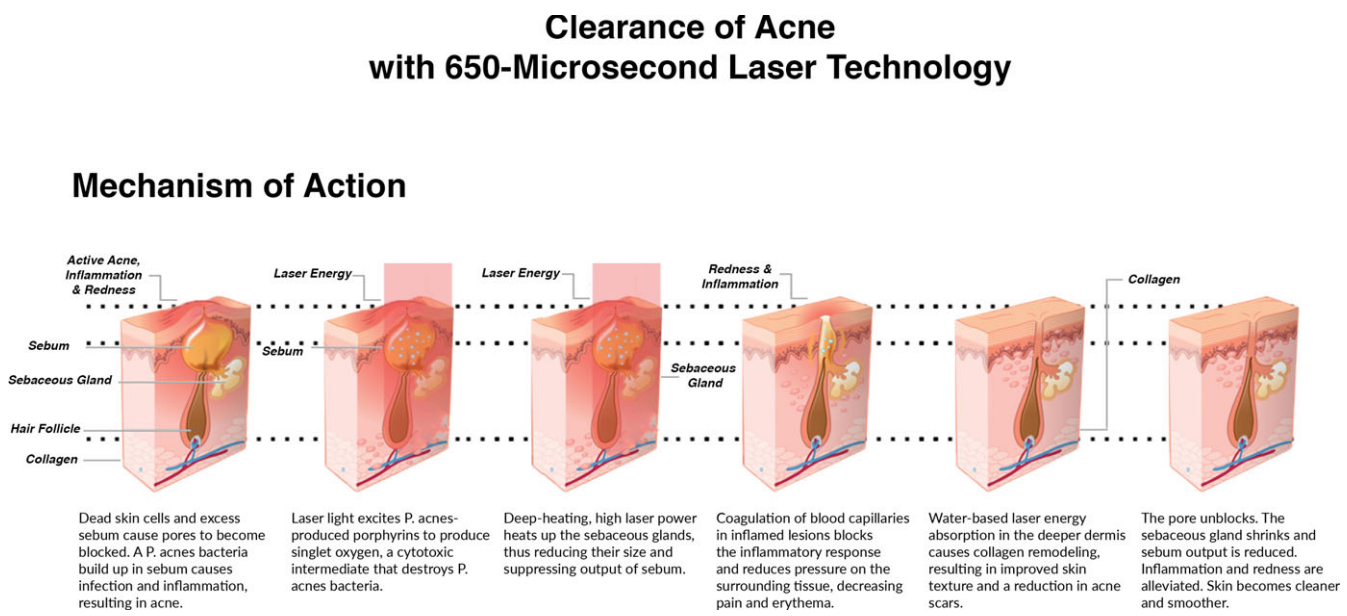

FIGURE 1 Steps by which the 650-μs 1064-nm Nd: YAG laser clears acne lesions. Courtesy of Aerolase Corporation, Tarrytown, NY

hyperproliferation of follicular epithelium which, in turn, prevents the formation of microcomedones and subsequent development of both inflammatory and noninflammatory acne lesions.[8,10,14,15] This assertion is supported by the work of Jain and Ahmed,[16] who showed that pretreatment of skin with adapalene enhanced the penetration of topical clindamycin phosphate, thus increasing the efficacy of the antibiotic. Tretinoin, adapalene, and tazarotene are the only retinoids approved for use in the USA.[13] Topical retinoids used alone are an excellent therapy for the treatment of predominantly comedonal acne.[13,17]

3.2 | Antibiotics and BPO

Topical antibiotics that target *P. acnes* are inexpensive and have minimal local side effects. Use should be limited, however, to changing resistance patterns in *P. acnes*.[13] Clindamycin antibiotic has the additional advantages of anti-inflammatory and anticomedogenic effects. Topical BPO targets *P. acnes* and has anti-inflammatory effects but weak activity against comedones.[8,18,19] The advantage of BPO over antibiotics is that it is not associated with antimicrobial resistance.[13,18] BPO (2.5%-10%) is available over the counter as a gel, lotion, cream, or wash.[13]

Antibiotic resistance in dermatology has been reviewed in detail.[13,20-22] Although dermatologists comprise only 1% of all physicians, they prescribe 4.9% of antibiotics, mainly for the treatment of acne. Since 1978, resistance of *P. acnes* has increased from 20% to approximately two-thirds. For mild to moderate acne, alternative topical treatments include salicylic acid, azelaic acid, and dapsone. Systemic options include low-dose isotretinoin and oral zinc. For moderate to severe acne, other first-line treatments include oral isotretinoin and a subantimicrobial dose of oral antibiotic in combination with topical therapies used to treat mild to moderate acne. Physical modalities (phototherapy, photodynamic therapy [PDT], chemical peels) may be effective in moderate to severe acne against inflammatory acne lesions.[13]

Started in 2005, the Scientific Panel on Antibiotic Use in Dermatology (SPAUD) was organized to promote antibiotic stewardship among dermatologists worldwide.[20] In their three-part series,[20-22] Del Rosso et al. described antibiotic prescribing patterns, sources of antibiotic exposure, and other issues related to antibiotic use. For the treatment of acne, the authors concluded that dermatologists should (1) use topical antibiotics only when clinically indicated, (2) avoid antibiotic monotherapy, (3) use antibiotic in combination with BPO to minimize emergence of antibiotic-resistant *P. acnes*, (4) use oral antibiotics only when absolutely needed and in combination with topical therapies that preferably include a retinoid and BPO (and then only for 3-4 months and an "exit strategy"), and (5) consider nonantibiotic alternatives when starting treatment or adjusting therapy.

3.3 | Systemic antibiotics

The Guidelines of Care for the Management of Acne Vulgaris Work Group[17] recommends that systemic antibiotics (doxycycline, minocycline, tetracycline) be used to manage moderate to severe acne and forms of inflammatory acne that resist topical therapies. Treatment should be limited to 3-4 months and followed by topical retinoids or BPO to minimize the development of antibiotic resistance. Monotherapy with systemic antibiotics is discouraged for the same reason. Use of antibiotics other than the tetracyclines is not recommended due to the limited data available for the treatment of acne.

3.4 | Combination therapy

To limit antibiotic resistance, the Global Alliance has recommended the use of a fixed-dose combination of topical retinoid and an

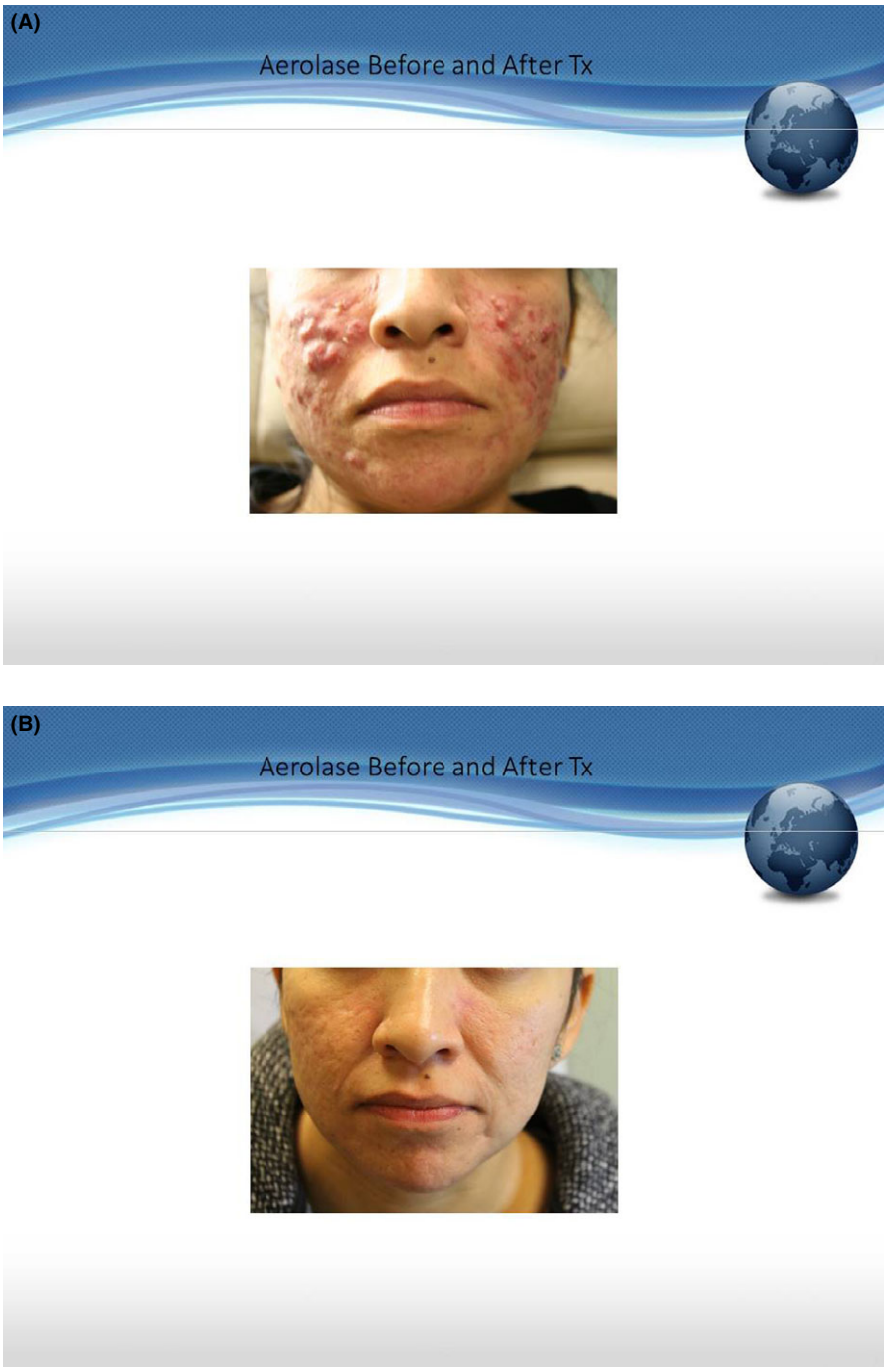

FIGURE 2 A 27-year-old female before (A) and 13 months after 6 treatments with the 650-μs 1064-nm Nd: YAG laser (B). Courtesy of Michael H. Gold, MD

antibiotic rather than an antibiotic alone for most acne patients.[10,23] The mechanisms of action of these individual agents target three of the four pathogenic factors of acne—keratinization (follicular plugging), colonization by *P. acnes*, and inflammation. The result is more effective clearance of both inflammatory and noninflammatory acne lesions than with either agent alone.[8,10]

As with systemic antibiotics, the duration of combination therapy that includes antibiotic should be limited to 3-4 months[10] and substituting BPO when long-term use of antibiotic is indicated. The latter recommendation is based on the bactericidal effectiveness of BPO and the minimal development of resistance to BPO at application sites.

In response to these recommendations, the use of fixed-dose adapalene in combination with BPO has been explored recently in 2,780 young adults and adolescents with moderate inflammatory acne,[24] 73 Brazilian patients with papular-pustular acne,[25] more than 2,300 patients with inflammatory and noninflammatory lesions by meta-analysis,[26] and 503 patients with moderate and severe acne in

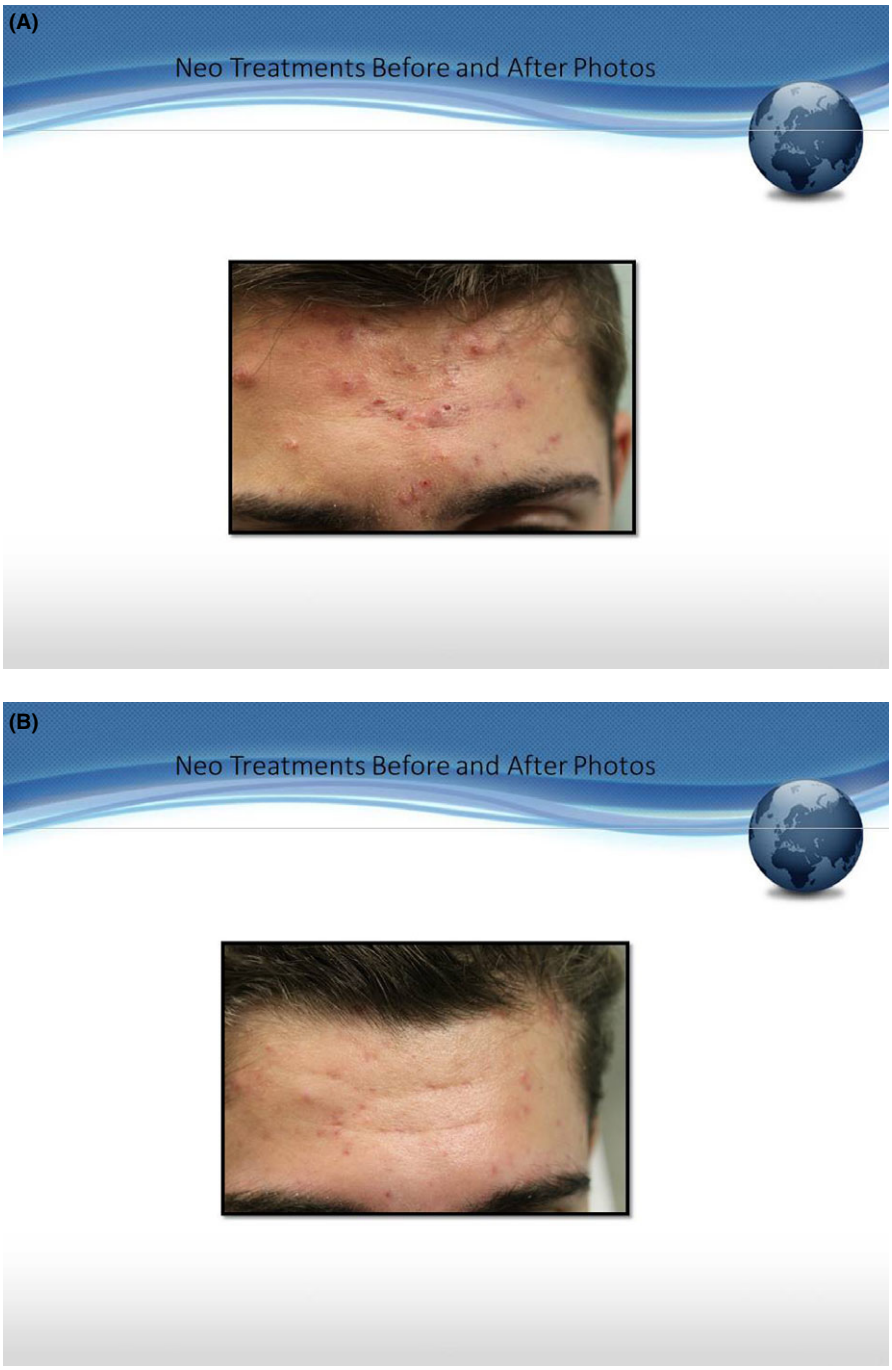

FIGURE 3 A 17-year-old male before (A) and after two treatments with the 650-μs 1064-nm Nd: YAG laser (B). Treatments were spaced 4 weeks apart. Courtesy of Michael H. Gold, MD

31 centers.[27] Advantages of this fixed-dose combination are that it is efficacious, well tolerated, useful in all forms of acne, not associated with antibiotic resistance, improves quality of life, reduces factors associated with adherence, and can be used for long-term treatment of chronic acne.[28]

The use of a fixed-dose combination of clindamycin (rather than adapalene) and BPO has also been explored in 498 patients with moderate to severe acne,[29] 800 Japanese patients with inflammatory and noninflammatory lesions,[30] 498 males vs. females with moderate to severe acne,[31] 72 adult females with moderate to severe acne,[32] 298 adolescents with moderate to severe acne,[33] and 498 patients with moderate to severe acne.[34,35] The combination is well tolerated and particularly useful in adult females, adolescents, and other populations with moderately severe disease.[29]

Other fixed-dose combinations without BPO (which can bleach hair) and fabrics include clindamycin with tretinoin[36] and hydrogen peroxide and salicylic acid with D-pantenol.[37] The latter combination is well tolerated, even during sun exposure. A combination of retinoid,

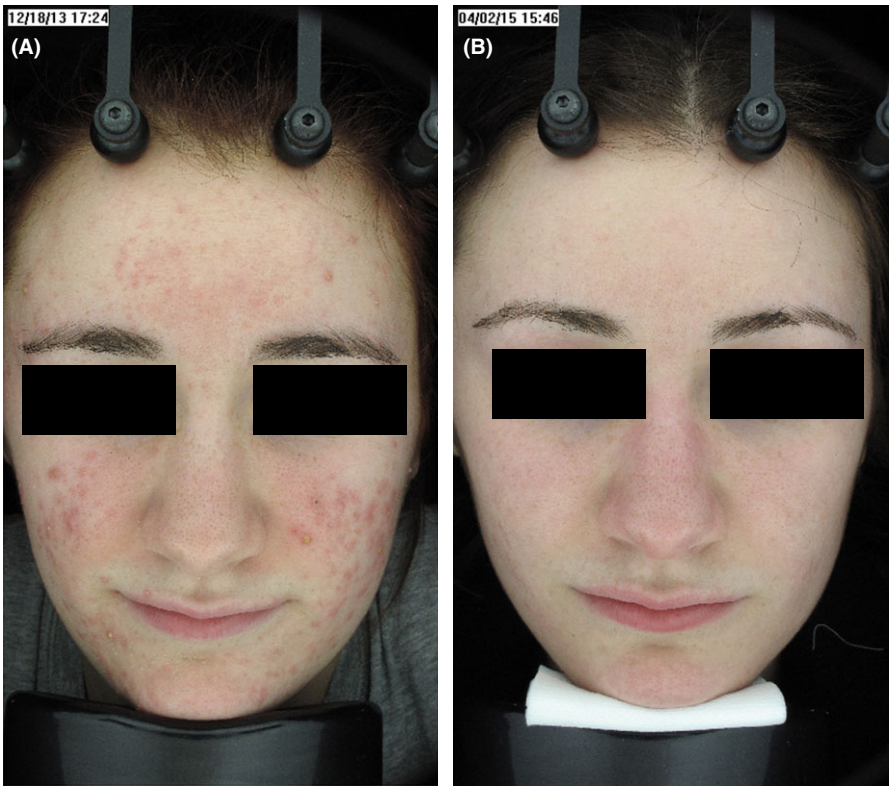

FIGURE 4 A 22-year-old female before (A) and after five treatments (B) with the 650-μs 1064-nm Nd: YAG laser. Treatments were spaced 2 weeks apart. Courtesy of David J. Goldberg, MD

alpha-hydroxy acid, and salicylic acid was recently reported[38] because it takes advantage of differing mechanisms of action against acne.

3.5 | Isotretinoin

Isotretinoin, a highly effective treatment option for moderate to severe acne, acts by shrinking sebaceous glands.[13,39] Isotretinoin is appropriate for acne resistant to other treatments, nodulocystic inflammatory acne, and acne fulminans.[40] Patients experience decreases in sebum production, acne lesions, acne scarring, and reduced anxiety and depression.[17] After 4 months of treatment, patients experience 80% to 90% reduction in acne lesions and prolonged remission of 70% to 89% during 2 to 4 months after treatment stops.[40] Side effects include musculoskeletal aches, elevated triglycerides, cheilitis, and ophthalmic symptoms. The teratogenic effects of isotretinoin require female patients to participate in the iPLEDGE system.[13,17]

3.6 | Hormonal therapy

Androgens and their receptors are the primary targets of systemic hormonal therapies for the treatment of acne, particularly in females.[41] Androgens regulate production of sebum and acne formation in both sexes.[42,43] Most are produced by the adrenal glands and gonads and some are produced at the sebaceous gland level as well. Adrenal and gonadal androgens are converted to testosterone and dihydrotestosterone by type I 5α-reductase, an enzyme found in the follicular infundibulum of the sebaceous gland.

Most candidates for hormonal therapy are women with signs of hyperandrogenism who respond poorly to topical therapy for their acne, flares of facial acne prior to menstruation, and deep nodules of the neck and face.[44] The goals of hormonal therapy are to suppress production of androgens in adrenal glands, ovaries, and the pituitary gland, and to block androgen nuclear receptors on target cells, keratinocytes, and sebocytes.[43,45,46] Hormones therapy may be used in combination with antibiotics, BPO, azelaic acid, and retinoids. Improvement may not become apparent for up to 3 months,[43] and efficacy is well established even if androgen levels in serum are not elevated.[46] Hormonal agents used in the treatment of acne are shown in Table 1.

3.6.1 | Androgen receptor blockers

Spironolactone, though not FDA approved for the treatment of acne and whose efficacy in acne is considered "indeterminate" by the Cochrane review group,[47,48] is well tolerated by women and has been used off-label for more than 30 years to treat acne and hirsutism.[43,44,46] Spironolactone is contraindicated in pregnancy because of potential feminization of a male fetus and may be used by women unable or unwilling to take combined oral contraceptives.[46]

Flutamide is FDA approved for the treatment of prostate cancer. A nonsteroidal androgen receptor blocker, flutamide is

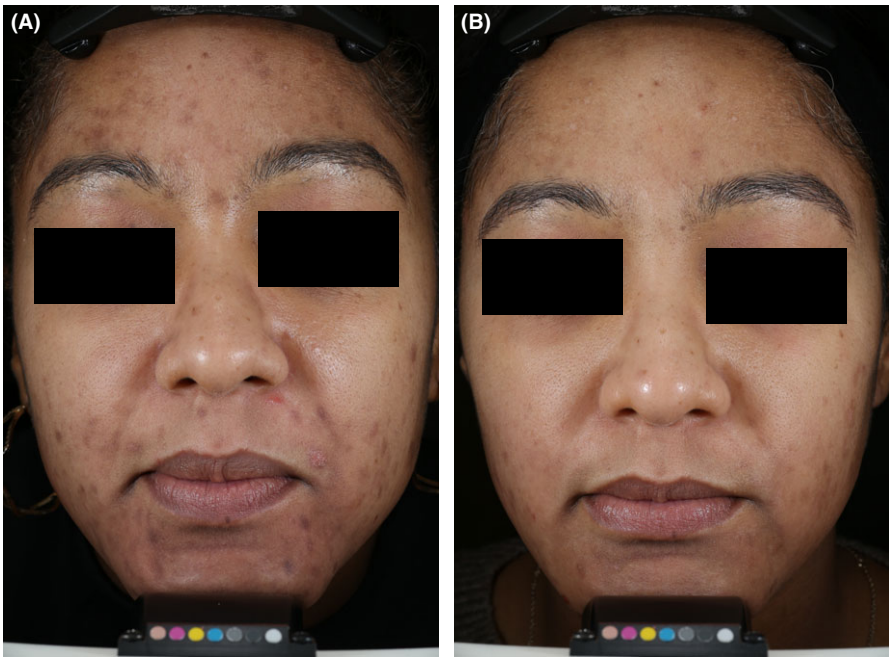

FIGURE 5 A 33-year-old female before (A) and after four treatments (B) with the 650-μs 1064-nm Nd: YAG laser. Treatments were spaced 2 weeks apart. Courtesy of David J. Goldberg, MD

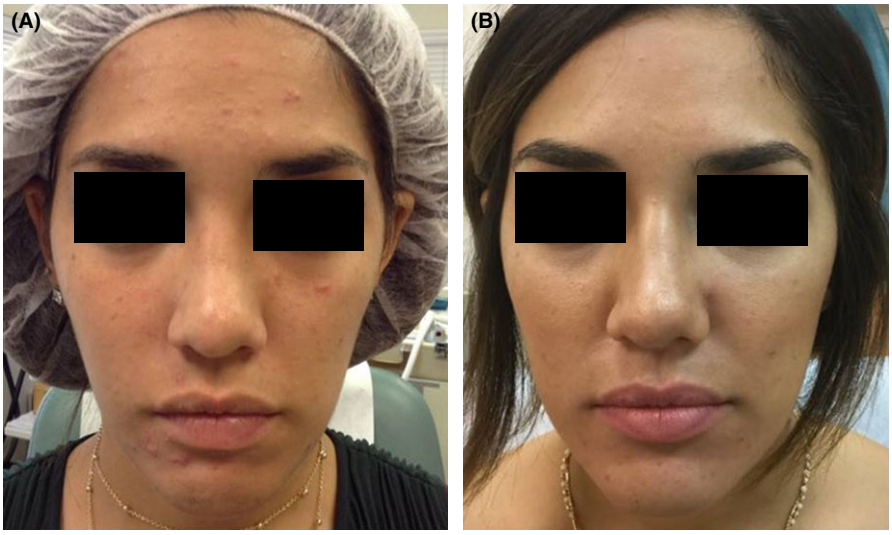

FIGURE 6 A 32-year-old female before treatment (A) and 2 months after four treatments with the 650-μs 1064-nm Nd: YAG laser (B). Treatments were spaced 2 weeks apart. Courtesy Mark S. Nestor, MD, PhD

contraindicated in pregnancy but is effective against acne, hirsuitism, and androgenic alopecia. Cyproterone acetate, an anti-androgen and a progestin, may be used alone or in combination with ethinyl estradiol to treat acne.[43,44] Cyproterone acetate shows high improvement in acne when used alone.[43,49]

3.6.2 | Oral contraceptives

Combined oral contraceptives used to treat acne contain cyproterone acetate, chlormadinone, drospirenone, and an estrogen, usually ethinylestradiol.[46] Three oral contraceptives (Estrostep, Warner Chilcott company, Inc., Fajardo, Puerto Rico; Ortho-Tri-Cyclen, Ortho-McNeil Pharmaceutical, Inc., Raritan, NJ; and Yaz, Bayer Healthcare Pharmaceuticals Inc., Wayne, NJ) are approved by the FDA for the treatment of moderate acne in menstruating females at least 14 or 15 years of age.[50] Six additional combined oral contraceptives are also effective against both inflammatory and noninflammatory facial acne lesions.[51] Oral contraceptives reduce androgen levels and block production of sebum. They are useful in women who have acne and desire contraception. Oral contraceptives are contraindicated in patients with a history of venous thromboembolism, heart disease, genetic clotting disorder, severe obesity, liver

TABLE 1 Hormonal agents used in the treatment of acne [41,43,44,46]

Agent	Action	Side effects	Comments
Spironolactone	Block androgen effect on sebaceous gland, inhibits 5α-reductase enzyme	Hyperkalemia, menstrual irregularity, breast tenderness or enlargement, birth defects, neurological and gastrointestinal effects	Limited use in men due to reduce libido, impotence, gynecomastia; used in combination with oral contraceptives; available as oral medication or topical cream
Flutamide	Block androgen effect on sebaceous gland	Breast tenderness, hot flashes, reduced libido, gastrointestinal distress, fatal hepatitis	Feminization of male fetus; use in acne limited due to cost and potential hepatotoxicity
Cyproterone acetate	Block androgen effect on sebaceous gland	Headache, nausea, breast tenderness, breakthrough bleeding, hepatotoxicity	Feminization of male fetus, pseudohermaphrodite condition
Oral contraceptives	Suppress production of androgens by ovaries	Increased risk of thromboembolism, myocardial infarction; potential risk of breast cancer	Improvement in acne may require 3 months, acne may reappear after therapy stops
Flucocorticoids	Suppress androgen production by adrenal glands	Risk of osteoporosis, abnormal blood sugar, adrenal suppression	Preferred use limited to 6 months
Finastride	5-α reductase inhibitor	Potential fetal feminizing effect	5-α reductase reduces testosterone to dihydrotestosterone, a more potent androgen

disease, hypertension, smoking (women over 35), diabetes mellitus, pregnancy or breastfeeding, immobilization for extended periods, history of cancer, and migraine headache.[44]

3.6.3 | Other agents

Glucocorticoids are useful in the treatment of congenital adrenal hyperplasia. Finastride, the only agent marketed as a 5α-reductase inhibitor, is also used to treat male pattern baldness and is under investigation for the treatment of acne.[44]

3.7 | Intralesional injections

Triamcinolone acetonide is often injected into large, nodular acne lesions.[17,52,53] The purpose is to quickly provide a highly concentrated steroid within the lesion with minimal systemic absorption.[54] The procedure is simple, inexpensive, and has limited side effects.[55] Patients experience reduced pain and rapid improvement in the injected lesion. Temporary improvement at sites distant from the injected lesion as well indicates systemic absorption of steroid and suppression of the adrenal gland androgens.[17,52,55] Local skin atrophy, pigmentary changes, and telangiectasias may be observed with intralesional injections.[13,17,54,56]

4 | LIMITATIONS OF TOPICAL AND ORAL AGENTS

The clinical usefulness of topical and oral agents for the treatment of acne vulgaris is often less than ideal because of their slow onset of action, limited efficacy in some patients, side effects (leading to reduced adherence), and the potential development of antibiotic resistance.[57] In addition, 81% of women report failure with systemic antibiotics and recurrence has been noted in 15% to 30% of patients after isotretinoin.[58] Improvement in acne may require up to 3 months with oral contraceptives[44] and the complete effect of these agents in acne is apparent at 6-9 months.[46]

Topical retinoids, except for specific new formulations, are associated with erythema, scaling, burning, dryness, and pruritis in up to 75% of patients.[8,59] These agents are also contraindicated in pregnancy, forcing patients of childbearing age to use contraception during treatment.[8,60]

As monotherapy, antibiotics are not recommended by both the Global Alliance and the European Dermatology Forum because of the increasing problem of antibiotic resistance[10,23,61] and the availability of clinically superior regimens.[23] Resistance varies among antibiotics and geographic location, and multidrug resistance is widespread as well.[23,62-64] The drawback of BPO is a cutaneous irritation or dermatitis that may occur at high concentrations.

Another problem with topical and systemic agents is adherence of patients to their treatment which, for acne (a chronic disease), may be prolonged. In a 3339-patient study of acne patients in Europe, the Americas, and Asia, adherence to acne medications was 58%, 48%, and 43%, respectively. These poor adherence rates were attributed in part to side effects of medications, lack of dermatologist-evaluated improvement, and lack of patient satisfaction with treatment.[65]

5 | LIGHTS AND LASERS

It is well known that exposure to sunlight often improves acne[66] by a mechanism not yet understood. Arakane et al.[67] reported that in vitro irradiation of *P. acnes* colonies with blue light resulted in excitation of bacterial coproporphyrin and the production of

bactericidal singlet oxygen. These findings, together with concern with the development of bacterial resistance to antibiotics, led researchers[57,68-74] to further investigate the use visible light, particularly blue light, for the treatment of acne.

At the time of this writing, the efficacy and safety of light and laser therapies for the treatment of papular, pustular, and comedonal acne have been demonstrated by numerous clinical trials.[75] Yet clinicians must bear in mind that the natural tendency of acne to "wax and wane" creates a challenge when trying to study acne with lasers and lights. The authors therefore recommend that clinicians use lasers and lights in combination with systemic or topical medications to treat acne vulgaris.[76]

Detailed reviews of procedures for the treatment of acne vulgaris have been published.[54,75,77,78] A variety of studies show the effects of light of various wavelengths for the treatment of acne.

Ultraviolet (UV) light, natural or artificial, improves inflammatory acne lesions.[79] Long-term clearance, however, is lacking with UV light.[77] Other drawbacks are that penetration of UV light into the skin is limited and long-term exposure is carcinogenic.[77] Short-term narrowband UV-B, however, has been used successfully to treat acne vulgaris during pregnancy, thus avoiding the risk of harm to the fetus due to topical and systemic therapies.[75,80]

Visible light, particularly blue and red light, is effective against acne. The efficacy of blue light and red light may be understood by considering the 415-nm (blue) and 630-nm (red) absorption peaks of porphyrins (coproporphyrin III and protoporphyrin IX [PpIX]) produced by *P. acnes* in the sebaceous glands. Irradiation of light at these wavelengths elicits a photodynamic response in which the light excites *P-acnes*-produced porphyrins to produce singlet oxygen, a cytotoxic intermediate that destroys *P. acnes* in the sebaceous glands. The result is clearance of the inflammatory acne lesions.[81]

Several groups have shown that combinations of blue light and red light are effective against acne vulgaris. Red light penetrates deeper into the skin than blue light and exerts an anti-inflammatory effect because it modulates cytokine response.[82] Papageorgiou et al.[83] showed that a combination of blue light and red light resulted in 76% improvement in inflammatory lesions and 50% reduction in noninflammatory lesions in patients with mild to moderate acne. The authors suggested that the blue-red combination may have had a combined antibacterial and anti-inflammatory effect. Six years later Goldberg et al.[84] treated patients with moderate to severe acne repeatedly over 12 weeks, alternating between 415-nm blue light and 633-nm red light. At the end of the study, the mean lesion count was significantly reduced by 81%.

Blue-violet light continuous wave sources also excite porphyrins but acne clearance is variable and associated with high relapse rates after therapy stops. Light of various combinations (UV, violet, green, red, blue, white) affect mainly inflammatory lesions with little clearance of papules and comedones.[77] Nevertheless, studies with blue light alone have resulted in "very good" improvement of acne,[85] 55% reduction in acne lesions of all types,[69] 55% reduction in lesion counts,[86] and 36% reduction in pustules and papules.[87]

Intense pulsed light (IPL) is nonlaser broadband light that is polychromatic, noncoherent, and high-intensity.[75] El-Latif et al.[88] compared IPL to BPO gel for the treatment of mild to severe acne vulgaris. In this 50-patient study of skin type IV patients, both IPL and BPO significantly reduced inflammatory lesion counts after 5 weeks of treatment. Reduction in counts was significantly greater with BPO after 2.5 weeks, but the difference was not significant at the end of the study.

Elman et al.[89] obtained 74% clearance of inflammatory acne lesions and 79% clearance of noninflammatory lesions one month after a 4-week series of treatments with IPL. Kawana et al.[90] treated Japanese patients with moderate to severe acne with IPL at two wavelength ranges: 400-700 nm and 870-1200 nm. After five treatments, noninflammatory lesions decreased to 12.9% of their pretreatment values while inflammatory lesions declined to 11.7% of pretreatment values without serious adverse events.

Canavan et al.[13] suggest that the efficacy of 400- to 1200-nm IPL may be partly due to its longer wavelengths because sebum has an absorption peak of 1210 nm. As with other light treatments, long-term follow-up data for IPL are lacking which, for acne, is important as *P. acnes* levels remain low only if light treatments are applied over longer time periods, as with antibiotics.[91] Drawbacks of IPL include pain during treatment (with and without anesthesia), immediate erythema, burning, stinging, crusting, bulla formation, and hyperpigmentation.[92]

In 2009, the Global Alliance reported that laser and light-based therapy, including photodynamic therapy (PDT), are most useful as an adjunct to medical therapy or for patients unable or unwilling to undergo medical therapy. The authors further stated that these modalities reduced levels of *P. acnes* via excitation of light-sensitive porphyrins, disrupted the functions of sebaceous glands, and may act on inflammatory cytokines.[10] Light sources and lasers with wavelengths absorbed by porphyrins include narrowband and broadband light and pulsed dye lasers (PDLs) (585 nm), potassium titanyl phosphate (KTP) lasers (532 nm), and 610- to 635-nm lasers and light sources. Longer wavelengths (1320-1540 nm) are less absorbed by porphyrins but lasers in this range heat the sebaceous glands, thus reducing their size and output of sebum. Lasers in the near- and far-infrared are associated with pain.[10]

For the treatment of acne, data are available regarding the efficacy of narrowband blue light, the 585-nm PDL, and the 1450-nm diode laser.[10] Firm conclusions are difficult because patient numbers in the studies were small, treatment settings were variable, and results were inconsistent. Blue light was most effective against inflammatory lesions[10] and less effective against comedones.[93] Blue light does not penetrate deeply into the dermis, thus limiting its efficacy with deeper nodules and cysts.[93] Studies of blue light also show variable responses among patients, high relapse rates after therapy stops, and lack follow-up data longer than 12 weeks.[94] Pulsed dye laser (PDL) treatment with 585-nm radiation resulted in a 53% reduction in lesion counts,[95] and results were comparable to treatment with BPO.[96] The PDL is considered especially useful in the treatment of inflammatory acne lesions.[75] The PDL has been

studied alone and in combination with other devices with variable results in the treatment of acne. In a split-face study comparing PDL with IPL for the treatment of facial acne,[97] both modalities improved acne but the benefits of PDL persisted longer after the final treatment.

The 532-nm KTP laser provided 36% clearing of acne in one study and 60% to 70% in another study[77] but post-treatment flares, decreased clearance, and faster relapses were also noted when the laser was used alone. In a later study of patients with moderate acne, Bhaug et al.[98] achieved a 34.9% and 20.7% reduction in acne severity at 1 week and 4 weeks after four treatments. Four years later Yilmaz et al.,[99] in a study of patients with mild to moderate acne, reported 60% to 70% clearing after six treatments with the KTP laser.

Mid-infrared lasers have been used to treat acne in clinical trials.[77] These lasers (1320, 1450, and 1540 nm) target the depth of skin where sebaceous glands reside and have been classified as lasers that destroy sebaceous glands.[81] Treatment is accompanied by cryogen spray cooling to protect the epidermis.

Several groups have reported on the use of the 1320-nm Nd: YAG laser to treat acne. Orringer et al.[100], in a split-face study, reported a significant improvement in lesion counts of open comedones in patients with facial acne. Deng et al.[101] reported a 57% decrease in inflammatory lesions, a 35% decrease in noninflammatory lesions, and a 30% reduction in skin sebum level after six treatments with a fractional 1320-nm Nd: YAG laser.

Paithankar et al.,[102] using optimized heating and cooling parameters, evaluated the histological effects on the sebaceous glands and skin of a rabbit ear (in vivo) and human skin (ex vivo) after treatment with a 1450-nm laser. They also conducted a clinical study in which subjects with acne on the back were treated. The histological results showed thermal damage in the sebaceous gland area and no damage to the epidermis in both the rabbit ear and human skin. The clinical study showed a statistically significant reduction in lesion count on the treated area compared to the control area. The authors concluded that treatment of acne with the 1450-nm laser and cryogen spray cooling was at least feasible, and that treatment effect might be attributed to direct heating of the infundibulum.[77]

Numerous studies of the use of the 1450-nm laser for the treatment of acne followed. Treatments resulted 80% decrease in inflammatory lesions,[103] 53.5% reduction in total lesion counts,[104] 75.1% reduction in lesion counts which persisted for 12 months after the final treatment,[105] 67% reduction in lesion counts with a low-energy, double-pass technique to reduce pain during treatment,[106] 63% decrease in lesion count,[93] 64% decrease in acne grade in Asians,[107] and 53.2% reduction in lesion counts with a double-pass and low-fluence technique.[108]

In a more recent study,[109] the 1450-nm laser was shown to shrink sebaceous glands, reduce seborrhea, and, in many small uncontrolled studies, to improve inflammatory acne. Thiboutot et al.[10] reported reduced lesion counts on acne of the back after treatment with the 1450-nm laser. Treatment was also associated with pain in areas with many inflammatory lesions and required cooling during treatment.[93] A randomized, split-face, investigator-blinded trial[109] showed that, although both sides of the face improved, treatment with the 1450-nm laser did not decrease the inflammatory lesion count when compared with the control side of the face.

Two groups have examined the efficacy and safety of the 1540-nm Er: Glass laser for the treatment of facial acne[110] and moderate to severe facial acne.[111] Both studies are noteworthy for their duration of follow-up after the final of 4 treatments. In the study of Angel et al.,[110] the authors noted 71% reduction in acne lesions at 6 months, 79% at 1 year, and 73% at 2 years without side effects. Contact cooling was required during treatment. Bogle et al.[111] reported investigator-assessed improvement at 78% at 6 months and, after a single retreatment at 6 months, 80% at 9 months compared to 72% in patients without retreatment. Papules, pustules, and nodules all responded well. Authors of both studies suggested the use of maintenance therapy to prolong clearance.

6 | PHOTODYNAMIC THERAPY

In PDT, a photosensitizer is applied to the skin and allowed to incubate for a period of time during which the photosensitizer selectively accumulates in abnormal tissue. After incubation, the photosensitizer is activated by light in the presence of oxygen to initiate chemical reactions that destroy the abnormal cells.

The most frequently studied photosensitizing agent is 5-aminolevulinic acid (ALA) which selectively accumulates in cells of solar keratosis, squamous cell carcinoma, basal cell carcinoma and, in patients with acne vulgaris, the pilosebaceous unit. A natural precursor of heme, ALA, is converted to the photosensitive protoporphyrin IX (PpIX) produced by *P. acnes*. When exposed to light of the appropriate wavelength, PpIX becomes activated to produce singlet oxygen, the cytotoxic agent of ALA PDT. ALA is FDA approved for the treatment of actinic keratosis of the face and scalp, as is its methyl ester methyl aminolevulinate (MAL). Both compounds have been used with light or lasers to treat acne vulgaris. Patients most suitable for ALA PDT are those with inflammatory and cystic acne.[112,113]

6.1 | Evolution of PDT

A key study in the use of PDT to treat acne was reported in 2000 by Hongcharu et al.[114] The authors treated 22 subjects with mild to moderate acne of the back. Each subject was treated at four sites, one with ALA (20%) and red light (550-700 nm), another with red light alone, a third with ALA alone, and the fourth was not treated. ALA incubated 3 hours under occlusion and was then exposed to red light. Eleven subjects received one treatment and the other 11 received four treatments. In addition to acne clearance, the authors studied sebum excretion rates, histologic changes, protoporphyrin synthesis in pilosebaceous units, and auto-fluorescence from follicular bacteria before and after treatment.

Inflammatory acne vulgaris was cleared for 10 weeks in patients treated once with ALA PDT and for 20 weeks in patients treated 4 times with ALA PDT, showing that multiple treatments resulted in longer periods of clearance. The study also showed post-treatment damage to sebaceous glands and decreases in sebum excretion rates and bacterial porphyrin fluorescence in sebaceous follicles, all only in sites treated with ALA PDT. Side effects included transient superficial exfoliation, hyperpigmentation, and crusting.

The report of Hongcharu et al.[114] laid the foundation for subsequent studies in which other light sources were used to activate photosensitizers in the treatment of acne. Itoh et al.,[115] using a 635-nm pulsed excimer laser and incubating ALA 4 hours before laser treatment, demonstrated remarkable success in a single patient with intractable facial acne. The treated area remained free of disease for 8 months, although the patient experienced erythema, edema, and crusting (the PDT effect) immediately after treatment. One year later, Itoh et al.,[116] using 600- to 700-nm halogen light, reported improvement in inflammatory acne lesions that persisted for up to 7 months in 13 patients.

Reports with long ALA incubation times led investigators to try short-contact, full-face ALA PDT therapies. Goldman[117] treated acne vulgaris and sebaceous hyperplasia with 15-minute ALA incubation followed by activation by IPL or blue light. He noted "relative clearing" of inflammatory acne lesions after once-weekly treatments for 2-4 weeks without the PDT effect. Gold,[118] using 30- to 60-minute ALA incubation and high-intensity blue light, treated patients with moderate to severe acne. He reported 60% response rates (compared to 43% with blue light alone) with no adverse events. Goldman and Boyce[119] treated patients twice with blue light with ALA and without ALA and reported a 68% reduction in papule counts with the ALA-blue light combination compared to 40% reduction with blue light alone. ALA, when used, was incubated for 15 minutes. Taub,[120] using 15- to 30-minute ALA incubation and blue light, treated 18 patients with moderate to severe acne. After two to four treatments, 11 patients reported 50% improvement and five patients reported more than 75% improvement. Gold et al.[121] obtained a 72% reduction in acne lesions 12 weeks after treatment with 30-minute ALA and IPL without the PDT effect. Using ALA PDT with a 595-nm long-pulsed PDT, Alexiades-Armenakas[122] demonstrated complete clearance of cystic, inflammatory, and comedonal acne vulgaris with long-term follow-up. ALA incubation time was 45 minutes and patients used topical therapy during the study period. All patients achieved complete clearance which persisted up to 6.4 months without crusting, blistering, purpura, scarring, and dyspigmentation. The results of these studies suggested that short-contact ALA PDT is effective against acne vulgaris and may be associated with minimal PDT effect.

Reports continued to appear describing ALA PDT with IPL,[123–125] the pulsed dye laser,[122,126] the KTP laser,[127] intralesional ALA,[128] MAL photosensitizer,[129–135] and newer photosensitizers.[136–139] ALA PDT has also been used to treat Asian,[124,140,141] Korean,[142] Japanese,[115,116,143] African-American,[144] and Chinese[145–147] patients.

The Guidelines of Care for the Management of Acne Vulgaris Work Group[17] state that among laser and light therapies, PDT has the most data for the treatment of acne. Recent reviews[75,148,149] concluded that PDT is effective against acne and side effects are acceptable. An author of the present work (M.S.N.) uses microdermabrasion or photopneumatic therapy before ALA PDT to enhance penetration of ALA. Activation is achieved by short-pulse PDL or blue light. After three treatments patients experience significant improvement which includes complete clearing of severe acne lesions. Results have persisted for 10 years or longer after treatment.[113]

Canavan et al.,[13] however, reported that pain and burning are relatively high in patients treated with PDT. Three groups[17,148,149] agreed that additional studies are needed to more precisely determine the optimal types, incubation periods, and concentrations of photosensitizers; treatment parameters for light sources; and durations of light activation and incubation.

7 | VISIBLE LIGHT REVISITED

Turning again to visible light alone, the drawbacks of this modality are an increased risk of thermal damage to surrounding tissues and that 400-nm and 600-nm wavelengths, for example, are strongly absorbed by hemoglobin and melanin, thus limiting their effectiveness in dark-skinned patients. Longer wavelength light, to be effective, requires considerable energy to overcome reflection, scatter, and absorption by epidermal and dermal constituents.[150,151] Higher energies, in turn, may cause pain during treatment, even when accompanied by cooling and anesthesia during treatment.[151]

To overcome these limitations, researchers have investigated the use of a device combining vacuum and broadband pulsed light to treat the different targets of acne. With this device, gentle suction to the target area brings the sebaceous gland closer to the skin surface (and to the treatment tip), opens the pores, and mechanically removes the sebum and shed cells of the infundibulum of the sebaceous gland, all before exposure to broadband light. Antibiotics given at the same time can act against *P. acnes* in the sebaceous gland because the blockage of the sebaceous gland has been removed as shown histologically.[152,153] The vacuum also stretches the skin to decrease the concentration of competing chromophores, thus clearing a path for the broadband light to treat the sebaceous gland.[151,154] The blue component of broadband light destroys *P. acnes* and the infrared component produces an anti-inflammatory effect.[155]

Various investigators have reported on the efficacy and safety of this vacuum device (Isolaz, Solta Medical, Inc., Hayward, CA) for the treatment acne vulgaris.[92,151–155] The results of five studies are presented in Table 2.

Outcomes were favorable in most studies, particularly in those in which patients had mild to moderate acne. In two studies,[92,155] a few patients experienced a worsening of acne early in the treatment course. Wanitphakdeedecha et al.[155] observed the greatest improvement in patients with severe acne and only modest reduction in lesions counts and global improvement. Adverse effects were mild and transient.

TABLE 2 Efficacy and safety of a photopneumatic device with intense pulsed light for the treatment of acne

Reference	No. of patients	Acne Level	Results	Adverse events	Comment
Shamban et al.[151]	56	Mild to severe	Median acne clearance=3 (1-4 scale)	Mild erythema	-
Gold and Biron[154]	11	Mild to moderate	Significant reduction in both inflammation and noninflammatory lesion counts	Pain, erythema, edema	-
Wanitphakdeedecha et al.[155]	20	Mild to severe	Modest reduction in lesion counts and global improvement	Erythema, purpura	Greatest improvement in severe acne, acne worsened early in treatment course
Lee et al.[92]	20	Mild to moderate	Significant lesion improvement, reduced lesion counts	Erythema, purpura	Global clinical improvement in most patients; exacerbation in pre-existing acne in few patients
Narurkar et al.[169]	41	Mild to moderate	69% reduction in inflamed lesions, 41% reduction in noninflammed lesions	Slight discomfort; mild erythema, edema, hypo/hyperpigmentation, dryness, flaking, bruising	Photopneumatic technology in combination with profusion therapy using three topical agents

8 | THE 1064-NM ND: YAG LASER

Studies on the use of the 1064-nm Nd: YAG laser for the treatment of acne are scarce. Ballin and Uebelhoer[156] used this modality at low fluence to treat a patient with a several-year history of severe inflammatory acne. After 10 weekly treatments, the patient achieved nearly 100% clearance of active acne lesions without pain during treatments. Chun and Calderhead,[157] using a carbon-assisted Q-switched 1064-nm Nd: YAG laser, reported greater than 90% clearance in a 14-year-old female with moderate to severe pustular and cystic acne. Jung et al.[158] used a dual-mode of quasi-long pulse and Q-switched 1064-nm Nd: YAG laser with a topical carbon suspension to treat 22 patients. The authors reported 58.6% reduction in inflammatory lesions and 52.4% reduction in noninflammatory lesions of the face. In 2016, Mohamed et al.[159] reported a randomized, single-blinded, controlled, split-face study comparing IPL with a long-pulsed 1064-nm Nd: YAG laser for the treatment of mild to severe facial acne vulgaris. Topical lidocaine was applied before treatment and ice packs before and after treatment on both sides of the face. Reductions in inflammatory lesions were 67.1% and 70.2%, while noninflammatory lesion counts decreased by 18.3% and 19.3% for the IPL and 1064-nm Nd: YAG devices, respectively. Differences between the two modalities were not significant, and side effects were minimal on both sides of the face.

9 | THE 650-μS LASER

The 650-μs Nd: YAG 1064-nm laser is the result of interest in how the pulse duration can be varied to optimize outcomes in esthetic applications. The uses of nanosecond (Q-switched), microsecond (intermediate pulsed), and millisecond (long-pulsed) Nd: YAG lasers for nonablative dermal remodeling have been reported.[160] In 2004, a 0.30-ms (i.e, 300 μs) 1064-nm Nd: YAG laser was shown to nonablatively reduce erythema, improve skin texture, and provide electron microscopic evidence of new collagen formation in patients after three treatments. Treatments were given without cooling or anesthesia, and discomfort was minimal.[160] Since then, a 650-μs 1064-nm Nd: YAG laser (LightPod Neo®, Aerolase Corp., Tarrytown, NY) has been developed and used for hair removal[161] and treating skin of color,[162] onychomycosis,[163] and facial telangiectasias,[164] all without cooling or anesthesia. The advantage of this laser is that the 650-μs pulse duration is shorter than or equal to the thermal relaxation time of the therapeutic target, thus minimizing thermal damage to surrounding tissues, scarring, pigmentary changes, and pain during or after treatment. The long wavelength (1064 nm) is also well suited to treating darker skin types.[161,162,164]

The pulse duration of traditional 1064-nm lasers is between 5 and 30 ms, which greatly exceeds the 700-μs thermal relaxation time of skin tissue.[163,165] Such long pulse durations require that the target skin tissue be cooled continuously to minimize pain during treatment and damage to surrounding tissue. For onychomycosis, cooling is not practical because the nail is thick and its surface is uneven. The 650-μs laser, with its pulse width slightly less than 700 μs, does not require cooling and therefore represents a more viable treatment option for onychomycosis.[163] With this in mind, Hochman[163] treated 8 subjects with culture or stain-proven nail infections several times with the 650-μs laser. Nails were noticeably improved, and the treatment was well tolerated by all patients.

In 2013, Rose and Goldberg[164] reported their successful treatment of facial telangiectasias using the 650-μs 1064-nm Nd: YAG laser without cooling during or after treatment. The results showed 100% clearance in 10% of patients, ≥50% clearance in 75% of patients, and 0%-49% clearance in 15% of patients without epidermal damage or purpura. Previous studies[166,167] in which facial telangiectasias were treated with a 1064-nm laser with a longer (millisecond) pulse duration also reported favorable clearance rates, but these results were

accompanied by purpura,[166] low response by smaller vessels,[166] and blistering,[167] even with epidermal cooling during treatment.

The 650-μs 1064-nm laser is particularly advantageous in the treatment of patients with dark skin. As the pulse duration is shorter than the thermal relaxation time of both the blood vessels and the skin, the target is heated more rapidly than the rate heat is conducted to the surrounding skin, thus reducing damage and lowering the risk of pigmentary changes.[164]

A clinical study of the use of the 650-μs 1064-nm Nd: YAG laser for the treatment of moderate to severe acne has been presented.[168] Patients (n=100, aged <25 years, skin types II-III) received three treatments at 1-week intervals. Inflammatory lesions were treated using 28-64 J/cm^2 fluence, 2-3 mm spot size, and 0.65 Hz repetition rate. Pulses (5-15 per lesion) were stacked and directed to the center of each lesion and circular to its edges until the reddish lesions became pale blue. No anesthetic or precooling was administered prior or during the treatment and pain was "tolerable and minor" during treatment and reduced after the procedure. Inflamed lesions became smaller in size and volume and acne scars appeared less severe. Patient satisfaction was high due to the rapid and esthetically pleasing results. Hyperpigmentation, burns, scars, and other adverse effects were not observed. The authors concluded that multiple laser pulses of high fluence and low repetition rate with the 650-μs 1064-nm Nd: YAG laser was a safe and effective treatment of moderate to severe acne. The mechanism by which the 650-μs laser clears an acne lesion is presented in Figure 1. Moving left to right, the pore becomes blocked and results in inflammation and redness. The laser light induces the formation of singlet oxygen, a cytotoxic intermediate that destroys P. acnes bacteria. This is followed by shrinkage of the sebaceous glands, coagulation of blood capillaries, reduction of erythema and pain, and stimulation of collagen remodeling to produce smoother and clearer skin.

Clinical results obtained by the authors are presented in Figures 2 through 6. Visible improvements are apparent in each case after 2 to 6 treatments (spaced 2 to 4 weeks apart) with the 650-μs laser.

10 | CONCLUSION

The use of light and lasers for the treatment of acne has become a mainstay in the treatment of severe acne and in patients not suitable for topical and systemic treatments. The novel 650-μs 1064-nm laser shows promise in the treatment of moderate to severe acne without pain during treatment and with minimal adverse effects, even on darker skin tones.

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