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Review Article

Light-based treatments for acne

痤瘡的光療法

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Acne is a common skin condition that can lead to significant scarring and psychological disturbance. The existing oral and topical anti-acne medications are limited by efficacy, adverse effects and patients' compliance. Lasers or light sources are explored as therapeutic options for acne. Light treatment targets the function of the pilosebaceous glands and reduction of *Propionibacterium acnes* that are pathogenic factors of acne. Patients whose acne is resistant to conventional treatments or who are intolerant to their side effects may be candidates for light treatment. Blue light, red light, pulsed dye laser, mid-infrared laser, intense pulsed light, photodynamic therapy have been studied in this regard. Long-term efficacy of light-based therapy is still lacking and careful selection of patients is necessary given its cost and discomfort.

痤瘡為常見的皮膚問題，卻可引致嚴重的疤痕及心理困擾。現存的口服及外敷藥物皆有著療效，副作用及醫囑依從性等各方面的限制，故激光或各種光源便被作為痤瘡的可行療法來探究。光療法針對痤瘡的致病原因，抑制毛囊皮脂腺功能並減少痤瘡丙酸桿菌數量以達致療效。對痤瘡常規療法無效或未能承受其副作用者，可視為光療法的合適人選。藍光、紅光、脈衝染料激光、中紅外激光、脈衝光（彩光）及光動力療法在痤瘡方面皆被受研究；但光療法的長期療效數據仍然匱乏，故必須因應其成本及過程不適的考慮來小心挑選治療患者。

Keywords: Acne, lasers, photodynamic therapy

關鍵詞：痤瘡，激光，光動力療法

Introduction

Acne vulgaris is one of the most common dermatologic disorders seen in clinical practice. The prevalence of facial acne in adolescents was 91.3% aged between 15 and 25 years and 52.2% had acne at the time of interview from a local surveillance study.[1] Severe acne can lead to negative psychological impact in adolescents and young adults, resulting from its effect on physical appearance. Severe inflammatory acne may also result in permanent scarring. The problem of acne sometimes continues into adulthood. Acne is a chronic inflammatory disease of the pilosebaceous units, associated with increased sebum production and hypercornification of the openings of pilosebaceous units.[2,3] Blockade of the follicular

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openings attract microaerophilic anaerobic bacterium, *Propionibacterium acnes*, that in turn induce follicular inflammatory response.

Medical therapies remain the gold standard of treatment for acne and provide adequate control for most but not all patients. However, their use is limited by adverse effects, slow onset of action, and inadequate long-term efficacy.[2] Most topical anti-acne therapy induces varying degree of irritation, dryness and occasional dermatitis. There is an increasing problem of antibiotic resistance of *P acnes* as a result of widespread use of topical and oral antibiotics for inflammatory acne, and this can lead to treatment failure.[3] The compliance of continual daily topical and oral treatment for weeks to months is also questionable. Isotretinoin is well known to be a teratogenic agent and female patients taking isotretinoin are required to adopt stringent contraceptive measures. It also has a number of mucocutaneous side effects such as chelitis and dry eyes. Therefore, alternative therapeutic options that are safe and effective remain to be desired by patients.

It had long been observed that sunlight exposure improves acne in 70% of patients. Previous studies have shown that UV light can improve acne but its use is limited by the carcinogenicity.[3] Lasers are increasingly popular in the past decade for treatment of various dermatoses and aesthetic purpose. A variety of lasers and light sources are now being tested for the treatment of acne. More patients are ready to pay a high cost on optical therapies for acne and acne scars. Blue light, red light, lasers and intense pulsed light (IPL) with photodynamic therapy (PDT) have found a useful niche in the treatment of inflammatory acne.[4,5] It is developed to provide patients with safer, effective and more convenient therapeutic option.

Mechanisms for treatment

The targets of light-based therapies are cutaneous *P acnes* and sebaceous gland.[6,7] These goals can be achieved via the photothermal and photochemical effects of lasers/light sources on selected chromophores in the skin.[8]

Targeting P acnes

Light destroys *P acnes* by targeting endogenous porphyrins. Irradiation of *P acnes* colonies with blue light leads to bacterial destruction *in vitro*.[3] *P acnes* produces and accumulates porphyrins (mainly protoporphyrin IV and coporphyrin III) that florescence under Wood's lamp or UV photography (Figure 1). Absorption peak of porphyrins occur at 415 nm (the Soret Band) at the near-UV and blue light spectrum and there are small peaks of absorption at 500-700 nm (Figure 2). Excited porphyrin molecules then generate singlet oxygen and free radicals.[9] These reactive oxygen species can damage the lipid layers of the bacterial cell wall and so reduce *P acnes* levels in skin. Red light with longer wavelength can penetrate more deeply into the skin but is less effective in activating porphyrins than blue light.[10]

P acnes destruction can also be enhanced by the use of a photosensitiser as *P acnes* produces more porphyrins than it normally produce when supplied with an exogenous source of 5-aminolevulinic acid (ALA).[7] Photoinactivation of P acnes depends on porphyrin concentration, wavelength of the photons, fluence of light sources, and temperature at which the reaction occurs.[10] The transient reduction in *P acnes* implies the prolonged anti-acne effect of PDT relies on factors independent of bacterial density. The strategy of *P acnes* eradication as therapeutic goal requires repeated treatments as the bacterium regenerates rapidly. Combination with topical agents such as topical retinoids should be used to reduce relapse.[7]

Targeting sebaceous glands

Suppression of sebaceous gland function is expected to have longer lasting anti-acne effect than *P acnes* reduction. The sebaceous gland can be selectively damaged partially by light energy, resulting in histological reduction of glandular size

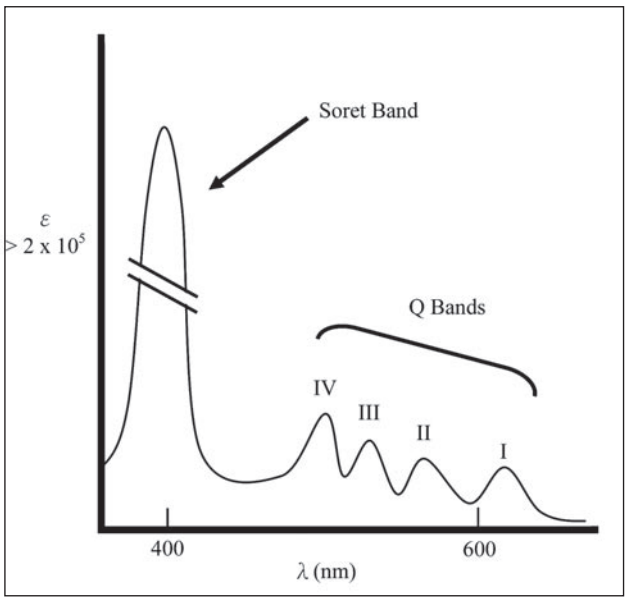

Figure 1. Light absorption spectrum of porphyrins. The Soret Band represents the highest peak of light absorption and thus highest sensitiser activation. Q Bands represent several weaker absorption bands at longer wavelengths.

and disruption of glandular function with decreased sebum production.[11] Whether light sources or lasers achieve the purpose depend on the depth of penetration of light energy, as sebaceous glands are mostly situated in the mid-dermis below 1 mm.[8] As photosensitisers are selectively absorbed and accumulated in the pilosebaceous units, photodynamic therapy (PDT) can target on both the sebaceous units and *P acnes* reduction.

Follicular obstruction may be altered by changing keratinocyte shedding and hyperkeratosis at the level of infra-infundibulum. This may partially explain the efficacy in acne given limited depth of penetration by lasers and the fairly short application time of ALA.[8,12] Besides, red light and pulsed dye laser also has anti-inflammatory effect by influencing cytokine release from macrophages that also influence the healing and wound repair.[3]

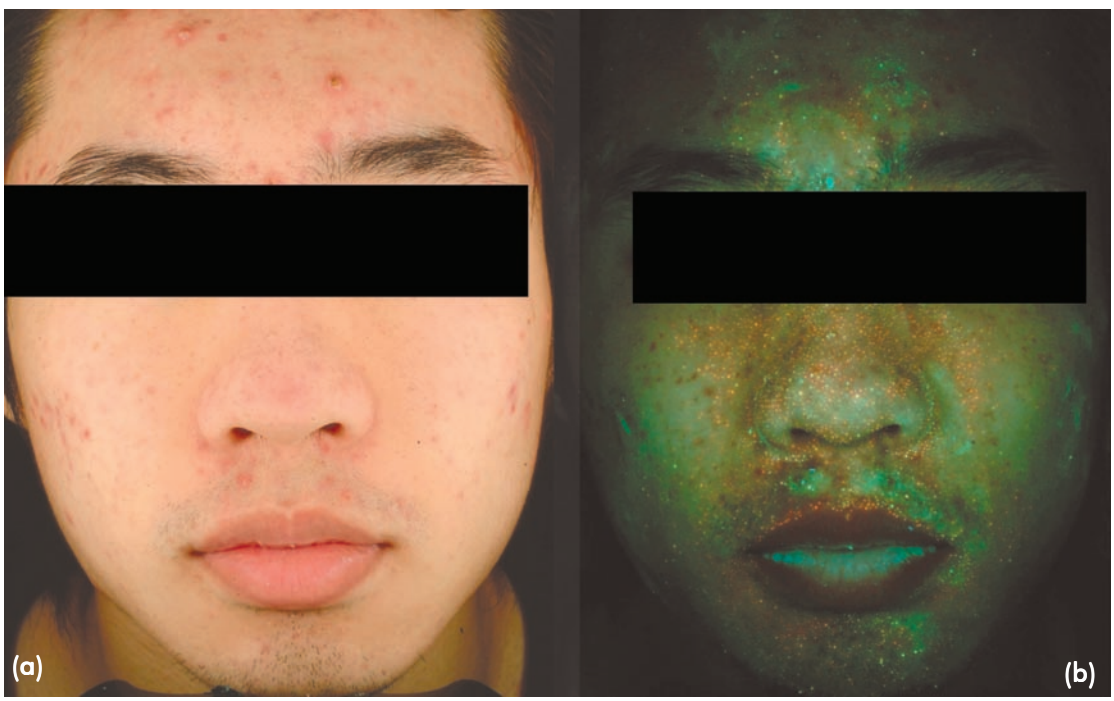

Figure 2. (a) Subject with moderate acne. (b) Fluorescence photography of acne showing numerous orange red punctate fluorescence corresponding to follicles and open comedones.

Selected modalities of light treatments

Incoherent light sources

A high-intensity narrow-band, blue light source (405-420 nm) has been developed for mild to moderate inflammatory acne. Treatments often last for 15 minutes twice weekly for 4 weeks. Kawada et al reported 64% reduction in mild to moderate acne in 30 patients on 5 weeks of therapy.[13] The effects are largely on inflammatory lesions rather than comedone formation. The blue light source showed clearance of acne comparable to topical 1% clindamycin lotion in one study.[14]

Blue light covering the Soret Band is more effective in photoactivation of porphyrins, but it is limited by the depth of percutaneous penetration owing to its short wavelength. Red light (635 nm) can penetrate deeply but less effective in photoactivation. Thus, the combined red and blue light seems to be more effective than either light source because of the synergistic anti-inflammatory and anti-bacterial actions.[3] Papageorgiou et al evaluated 4-week daily treatment with blue light and mixed blue-red light for mild to moderate acne and compared their efficacy with white light and benzyl peroxide 5% cream. At 12 weeks, the mixed blue-red light had the best improvement of 76% compared with blue light, white light or benzyl peroxide alone.[15] The advantages of narrow-band light source are its lower cost, more uniform illumination and larger areas of treatment. The efficacy of blue light is modest and variable with percentage reduction of acne lesions in the range of 30-60% compared to the baseline for inflammatory lesion count.[5,6,9] The relapse rate is high after therapy is discontinued.[8]

Photodynamic therapy

Photodynamic therapy (PDT) is a photochemical reaction requiring the presence of a photosensitising molecule, photoactivating wavelengths of light and tissue oxygen.[16] The process generates reactive, free radical intermediates that damage the target tissue. For the treatment of acne, topical 5-aminolevulinic acid (ALA) is applied for 0.5 to 3 hours with or without occlusion. Sebaceous glands and hair follicles selectively take up and convert topical ALA into photosensitizing protoporphyrin IX (PpIX), especially in inflamed acne lesions. PpIX can then be activated by appropriate light source.

New derivatives or vehicles of ALA such as methyl aminolevulinate (MAL) have been developed for use in PDT, with the potential benefits of higher lipophilicity and better penetration of the stratum corneum and lesional specificity.[17] Liposomes in spray form to encapsulate and carry 5-aminolevulinic acid (ALA) into the epidermis has been studied. Liposomes as vehicles can enhance penetration of ALA and enable a reduction in the concentration of topical 5-ALA by forty folds to 0.5% and so the phototoxicity after the procedure can be drastically reduced.[18] Activating light sources, including red, blue, intense pulsed light, pulsed dye laser (PDL), and LED, have been shown to be effective in PDT for acne.[9,16]

Hongcharu et al used 20% ALA cream occluded for 3 hours followed by red light irradiation. Long-term lesion reduction in 22 subjects was demonstrated on the back.[11] They showed reduced sebum excretion, decreased follicular fluorescence and sebaceous gland size in skin biopsy as long as 20 weeks after multiple sessions of PDT. Side effects included temporary folliculitis, erythema and hyperpigmentation. Increasing number of clinical trials have demonstrated effectiveness of 50 to 60% acne improvement by ALA- and MAL-PDT, after one to three treatments every 3 to 4 weeks for facial and back acne with improvement up to 20 weeks.[5,12,16] Majority of studies showed benefit of PDT over light therapy alone but PDT tends to be more painful than light alone.[19]

The adverse effect of photodynamic therapy is significant if standard regime as for treatment of other dermatoses is used. It may occur during or

immediately after treatment, causing significant pain, erythema, edema, and initial flare of acne, burning, hyperpigmentation, exfoliation and prolonged photosensitivity. It is crucial to educate patients about the need for sun protection up to 48 hours after PDT. Kasche et al reported that 54% of ALA-PDT and 14% MAL-PDT patients had to stop irradiation prematurely because of pain, given the ALA incubation time was double that of MAL in this study.[20] PDT regime of lower fluences and multiple passes can alleviate the discomfort and pain.[16] A short incubation of ALA from 30 to 60 minutes is increasingly adopted and has shown comparable effectiveness with reduction of side effects.[21] Consensus guideline suggests that 30 to 60 minutes incubation of ALA without occlusion is adequate before photoactivation in acne therapy but the short contact time only allows PpIX formation in infundibulum and upper epidermis.[2] No study so far has demonstrated microscopic evidence of selective sebaceous gland damage after short contact ALA-PDT. Mechanisms other than *P acnes* reduction and damage of sebaceous gland may be present to account for the efficacy of short contact regime. About 20% of the patients did not responded to short-contact ALA-PDT.[21]

Application of indocyanine green (ICG) as a topical photosensitizing agent in combination to green light laser (810 nm) has recently been described and ICG is more selectively absorbed by the sebaceous glands and seems to be more selective in action with less associated adverse effects. Selective damage of sebaceous gland without significant epidermal change and long-term improvement in back acne up to 10 months post-treatment has been reported.[22] PDT can be a viable option for treating moderate to severe inflammatory acne in instances of failure or intolerance of topical or oral medications. The benefit of ALA-PDT is its greater effectiveness, simultaneous rejuvenating effect, and faster clinical response in a limited number of sessions compared with daily intake of oral medications. The adverse effects of PDT can be reduced by lowering the fluences, fractionating treatments and increasing the selectivity of the photosensitisers.

Infrared diode laser

The 1,450 nm laser in the infrared range selectively injures the sebaceous gland by heating water in the surrounding upper dermis with simultaneous cooling of the epidermis by cryogen spray.[12] It has been shown to improve inflammatory acne. Human acne study on male back showed alteration of sebaceous gland with significant reduction in lesion count after treatment by the 1,450 nm lasers.[23] There are inconsistent reports on whether the laser treatment can effectively reduce the skin sebum excretion rate.[24] It appears that 1,450 nm laser also works through direct heating of the infundibulm that might improve the outflow and reset the keratinisation pattern in the follicle.[8] Jih et al reported 75% mean lesion count reduction that were maintained at 12 month follow-up in a 20-patient study at fluences of 14 or 16 J/cm^2.[25]

One of the limitations of 1,450 nm laser is the procedural pain and post-inflammatory hyperpigmention (PIH) which is especially problematic for Asian skin. The PIH rate has been reported to be as high as 39% in a Singapore study using the standard parameters (spot size 6 mm, 11-12 J/cm^2, DCD 50 ms) as on Caucasian skin.[26] Alternative treatment parameters using multiple passes of lower fluences and shorter dynamic cryogen spraying have been found to effectively reduce PIH rate while maintaining efficacy in a local study for Chinese skin.[27] In this study, there was reduction of mean acne lesions, 29% ($p<0.01$) from baseline at 4 weeks and 40% ($p<0.03$) 6 months later (Figure 3). Forehead sebum production was reduced by 31% ($P=0.006$) after 6 months post treatment. The most common side effect, transient erythema and PIH rate, was limited to 3.8%. This laser also has dual benefit of improving acne scarring by initiating new collagen synthesis as a result of bulk tissue heating effect.[26]

Pulsed dye laser

The PDL devices emit light of 575 to 595 nm selectively absorbed by oxyhaemoglobin. The PDL activates bacterial porphyrins and causes selective photothermolysis of the dilated vasculature component of inflammation associated with acne.[6] It also helps to improve erythema and scars associated with acne. There are 2 randomized controlled studies using the same setting of low fluence 585 nm PDL (1.5 or 3J/cm^2, one pass, single treatment) revealing mixed results. Seaton et al reported statistically significant 53% reduction in inflammatory lesion counts twelve weeks after a single treatment versus only 9% in controls while Orringer et al reported no significant improvement.[8] Complete clearance of acne has been achieved in all 14 patients in one study, using 595 nm PDL with short contact ALA-PDT of 45-minute incubation, at mean follow up of 6 months up to 12 months, but all patients continued topical therapy during the study period.[28]

Intense pulsed light

Most devices emit in the range of 500-1,200 nm, mostly in 550-700 nm. Previous study has demonstrated the effectiveness of IPL-assisted ALA-PDT in acne over IPL alone.[5] After three sessions of treatment with the 20% topical ALA with 30-minute incubation period to right face and full facial IPL three weeks apart, there was more significant improvement of facial acne on the ALA-treated side.[21] Santo et al used a 3-hour incubation period in a comparative spilt-face study of topical ALA plus IPL versus IPL alone done twice 2 weeks apart for the treatment of acne.[21] At the sixth week after treatment, 10 out of 13 subjects (77%) had significant decreases in inflammatory acne without new lesion formation in the ALA-IPL treated half of the face, but no improvement was observed compared with the baseline in the IPL treated side. However, our group previously demonstrated IPL alone and with MAL cream was not more effective than use of topical retinoid

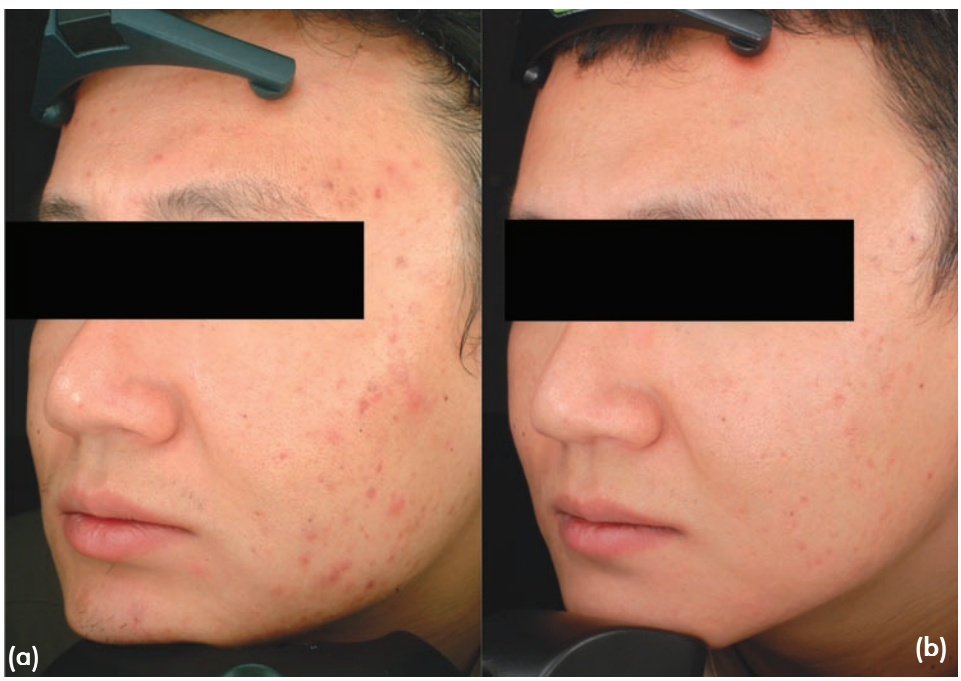

Figure 3. (a) Pre-treatment with multiple inflammatory papules and pustules on left cheek. (b) Three months after four treatments with the 1,450 nm diode laser. There is significant improvement in inflammatory acne.

alone in reducing inflammatory acne lesions in a randomized controlled split face study in Chinese.[29] IPL is not likely to be useful as a stand-alone treatment of inflammatory acne and multiple passes are required.

Limitation of current studies

From a number of systemic reviews, multiple sessions of lasers, blue light, mixed blue and red light with or without photodynamic therapy have been reported to be effective for acne lesions.[5] Nevertheless, results of the trials are conflicting, with range of likely outcomes from minimal improvement to 80% clearance of acne lesions at 3 months after 3-4 sessions of laser treatments.[8,10] There is a lack of quality studies in this field. Many of the studies are nonrandomized clinical trials involving relatively small number of patients, lacking in controls and had limited period of follow-up.[4,19] Few studies include histological changes after treatment for precise mechanisms for improvements. Evidence of long-term efficacy is still lacking. Adequate follow up beyond 6 months is important since recurrence is an important criterion for evaluating laser and light-based modalities which required multiple costly treatments.

The quality of studies is often compromised when the improvement was measured by comparing the post-treatment acne lesion count from baseline rather than controls, because of the disease's natural tendency to wax and wane.[21] Strong placebo is possible as there was 20-40% reduction of lesions on the control arm in many controlled studies, and concomitant topical agents were used in many of these studies.[19] Few studies compare the efficacy of the laser device with conventional medical therapies or focused on severe inflammatory acne. Besides, many patients in trials found that the side effects are unacceptable and discontinue the treatment despite small number of participants in individual studies.[19] Investigations involving more patients and longer follow-up periods and combining medical therapies are the future direction.

Clinical consideration

The existing light-based therapies rarely achieve complete remission and re-treatment is often necessary in around 6 months' time.[8,19] The treatments improve mainly the inflammatory acne such as papules and pustules, while non-inflammatory lesions such as comedones and cysts are generally resistant to light-based devices.[19] When considering use of laser, we have to balance the inconsistent benefits from laser or light sources with the established efficacy of conventional medical therapies. The preparation of laser procedure with the actual procedural time can be substantial, varying from 30 minutes to over 2 hours. The discomfort, downtime, sizeable time commitment and safety of light treatments have to be taken into account. The cost of light treatment is considerable and may not be covered by insurance plan.

The most effective regime achieving prolonged remission seems to use long application of photosensitizers with narrow band light sources or pulsed dye laser in the form of PDT.[2] However, this regime is associated with more significant side effects. There is a trend of using short contact ALA with low-fluence multiple-pass regime to achieve cumulative light doses adequate to reduce acne. The likely feasible approach is to combine light therapy with medical treatment as light therapy has faster onset of action while medical treatment prevents development of new lesions.

It remains uncertain which groups of patients benefit most from light treatment. It is likely that it serves as a complementary therapy given the existing effective anti-acne drug therapy. Light treatment may offer alternatives to conventional modalities in non-responders and noncompliant patients. Patients, who are unwilling or unable to take oral anti-acne medications such as oral

isotretinoin, are candidates of light treatments. For those patients reluctant to use oral treatment continuously and already have partial improvement with topical medical therapy alone, light therapy may achieve near complete remission in combination with topical therapy. It has more rapid onset of action, as quick as 2 to 4 weeks after first treatment, compared to conventional medical therapies and spare patients from the side effects of medical treatment.[4] The combination of ALA and photorejuvenation settings can also achieve acne clearance while simultaneously reducing dyschromias and acne scars.[8]

Patients are more likely to comply with light therapies because of the short treatment time notwithstanding initial procedural discomfort. Application of topical medication for back acne can sometimes be difficult and light therapy can be the treatment of choice. During the pre-treatment consultation, it is our task as clinicians to ensure realistic expectations from patients and their understanding of the limitations regarding the durability of treatment effect and the possible need of multiple clinic visits for repeated treatments. The patients should be informed of the potential side effects such as pain, PIH especially in Asian skin, and photosensitivity in PDT.

Conclusion

Although light-based therapies for acne offer promise, complete acne cure is still not achievable with current technology. Most light treatments produce temporary and incomplete acne remission and relapses are common. Therefore maintenance therapy is necessary with topical therapies and intermittent light treatments. It is best used as an adjuvant treatment to standard medical therapy or for patients who refuse or cannot tolerate medical therapy. Peri-procedural care including sunscreen and combined anti-acne therapy is also important in order to obtain optimal results.

The optimal device and settings for laser remain to be established. The rapid advances of light-based technology allow further research to clarify its role in acne treatment. To overcome the limited sustained efficacy, future development likely focuses on the highly selective light sources to the sebaceous units and more selective accumulation of photosensitisers in the pilosebaceous units, leading to substantial and irreversible reduction of sebaceous gland function.

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