Red and Blue Light for Acne
The Federal Trade Commission’s (FTC) recent shutdown of two anti-acne Smartphone apps drew a good deal of attention from the popular press and the medical community. According to reports, the makers of the apps, which flashed alternating red and blue light and sold for $1.99 each, argued with regulators that research supported the efficacy of red and blue light irradiation in acne management. The FTC, however, noted that the programs claimed to “cure” acne but had no direct evidence for those claims.

While it’s unclear what if any effect the apps would have on an individual’s acne, research does indeed suggest a beneficial effect of both blue and red light in acne treatment. Blue light in the 420-490nm range is shown to be antibacterial against P. acnes, while red light in the 640-750nm range is anti-inflammatory.

In clinical trials, irradiation of the skin with blue or red light alone produced modest improvement in acne, but best results appear to come from photodynamic therapy (PDT). PDT involves application of an appropriate photosensitizing molecule to the skin that is subsequently activated via irradiation by a suitable light source. Currently three PDT agents are available in the US: ALA + Blue Light (Levulan Kerastick, DUSA) is approved for AKs and has been studied for acne; mALA + Red Light (Metvixia, Galderma) is approved for AKs, BCC, and SCC in situ and has been investigated in acne. Allumera (Photocure) is a novel regimen with a cosmetic indication that has not been widely studied in other indications yet.

ALA is a precursor to protoporphyrin IX that, when exposed to light, generates reactive oxygen species that cause cell membrane damage. The official FDA indication for treatment of AKs calls for ALA incubation of 14-18 hours followed by blue light activation. Various off-label incubation times have been used, including as little as one hour. In some practices, microdermabrasion is provided prior to ALA application to enhance penetration of the agent.

For the treatment of acne, ALA PDT is thought to exert its effects through a number of proposed but unproven mechanisms. Reactive oxygen species are thought to provide a primarily antibacterial effect.

Take-Home Tips. Although light-base mobile apps for acne may be questionable, research suggests a beneficial effect of both blue and red light in acne treatment. PDT offers greatest promise. Most topical acne therapies are FDA indicated for use by patients 12 or older, therefore, treatment of the preadolescent patient is technically off-label. Emerging research is helping to support prescribing practices in preadolescents. Evidence now suggests that there may be sex-based differences in response to acne treatment, that moisturizing skin care supports topical acne therapy, and that new vehicles enhance penetration, reduce cutaneous adverse events, and improve adherence relative to older delivery vehicles. Old notions about tretinoin instability may be outdated.
while the treatment is also suspected to confer secondary anti-inflammatory benefits. There is evidence of decreased sebum production and reduction in sebaceous gland size following ALA PDT. In addition to the FDA-approved blue light source, ALA PDT is also provided using intense pulsed light (IPL). \(^1\)

A methyl ester of aminolevulinic acid, mALA (160mg/g) is applied under occlusion for a three-hour incubation period then activated by red light for the treatment of AK, SCC, and BCC. This three-hour incubation and irradiation protocol was reported effective for acne but was associated with severe phototoxic reactions.

Shorter mALA incubation may be associated with good efficacy and less severe phototoxic reactions. Ninety minute incubation with mALA (80mg/g) on the face followed by red light exposure provided a significant improvement in inflammatory lesion count for both occluded and non-occluded skin and high- and low-dose red light exposure of 25 or 37 J/cm.\(^2\)\(^,\)\(^3\)

Clinical trials are underway to further assess the efficacy of red light PDT in acne. In a recent presentation, R. Rox Anderson, M.D. provided an update on findings thus far. Red light is known to penetrate more deeply than blue light. It appears that while low-dose mALA/red light PDT confers a temporary anti-inflammatory effect, more aggressive mALA/red light may actually cause destruction of sebaceous glands and decreased sebum production. This ability to target the sebaceous glands may provide a long-lasting therapeutic effect and allow PDT to be used as an alternative to isotretinoin.

An intriguing protocol under investigation involves the use of both blue and high-dose red light PDT to treat acne. Low level blue light is applied prior to mALA application to inhibit porphyrin synthesis superficially in the epidermis and decrease the epidermal inflammatory reaction. After one to three hours of mALA incubation under occlusion, photoactivation is provided with a 635nm red light LED at ≥50J/cm\(^2\) fluence. Because this aggressive PDT approach is associated with pain, topical lidocaine anesthesia is provided. Other significant side effects associated with this protocol include erythema, edema, crusting, and pustules, which can last for several days. Light sensitivity after treatment may occur for 48 hours.

**Treatments for Preadolescent Acne**

It is not possible to ascertain the validity of anecdotal claims of an increase in the number of patients presenting with acne in preadolescence. Nonetheless, there is no question that dermatologists treat acne patients under the age of 12. Most topical acne therapies are FDA indicated for use by patients 12 or older, therefore, treatment of the preadolescent patient is technically off-label. While there has been little controversy associated with use of conventional topical acne treatments in this patient group, clinicians welcome research to support their prescribing practices.

A recent study has confirmed the efficacy and tolerability of tretinoin microsphere 0.04% gel (Retin A Micro, Ortho Dermatologics) in patients ages eight to 12.\(^5\) The 12-week study involved 40 patients with mild to moderate acne vulgaris who applied topical tretinoin microsphere 0.04% gel once daily. At week 12, the majority of patients (~75 percent) were rated as having only mild involvement or being almost clear. Treatment was well-tolerated with only mild cutaneous adverse events reported, mostly during the first three weeks of therapy.

**Sex Differences in Acne Therapy**

Increasingly, attention has focused on possible differences in acne in females compared to males. For example, female acne patients have been shown to report worse quality of life than male acne patients.\(^6\) In terms of acne presentation, it is generally accepted that nodulocystic acne is more prevalent in male patients,\(^7\) while specific distribution patterns of lesions may be associated with hormonally mediated acne in females.\(^8\) Evidence now suggests that there may be sex-based differences in response to acne treatment. An analysis of data from the phase III randomized trials of topical dapsone gel 5% (Aczone, Allergan) for acne vulgaris showed that female patients had a more significant decrease in inflammatory, non-inflammatory, and total acne lesion counts. The analysis involved 2,988 patients evenly distributed between active treatment and vehicle controls: 53.1
percent of the controls and 51.8 percent of the treat-
ed subjects were female.9

A higher percentage of female patients achieved
treatment success compared to male patients. There
was no gender difference in the incidence of adverse
events reported by treated patients. The difference
in response between treated females and males was
evident at all visits beginning at week 2 through
week 12.9

Topical Moisturizers and Topical Medications
The issue of non-prescription skincare use and topical
acne medications presents some clinical concerns. It
is known that poor tolerability of medications con-
tributes to non-adherence, as does a complicated
treatment regimen.10

On the one hand, regular use of a moisturizing
lotion is expected to increase skin hydration and sup-
port stratum corneum integrity.11 Moisturizers can
relieve cutaneous symptoms of dryness and peeling
associated with certain topical acne therapies.12
Therefore, use of moisturizers in conjunction with
topical acne medications has been advocated as a
rational strategy to reduce the irritating effects of a
topical medication, improve treatment tolerability,
and possibly support adherence. However, the effects
of moisturizer use in conjunction with topical acne
medications has not been extensively studied or docu-
mented in controlled trials. Furthermore, even if the
moisturizer enhances therapeutic compliance, adding
skincare is an extra step in the patient’s regimen.

A small study confirms that use of a topical mois-
turizer in association with topical acne therapy can
improve treatment tolerability. A trial of 119 patients
with mild to moderate acne vulgaris assessed the
impact of application of topical moisturizer on tolera-
bility of and adherence to tazarotene cream (Tazorac,
Allergan) therapy. Patients were randomized in
approximately a 1:2 fashion to apply either tazarotene
cream alone QPM (n=39) or moisturizer BID plus
tazarotene cream QPM, 20 minutes after moisturizer
(n=80).13

The reduction in inflammatory and non-inflamma-
tory lesions was similar in both treatment arms, indi-
cating that the moisturizer did not negatively influ-
ence treatment efficacy. While not statistically signifi-
cant, there was a trend toward reduced peeling and
erythema and consistently less dryness overall in the
moisturizer arm. Of note, the reduction in dryness did
achieve statistical significance at week 2, during the
period of retinization.

New Vehicles and Clinical Benefits
In light of the paucity of new chemical entities
approved by the FDA for dermatologic indications,
some skeptics have dismissed new vehicle formula-
ations as marketing tools. However, evidence suggests
that many new vehicles enhance penetration and
reduce cutaneous adverse events relative to older
delivery vehicles.

One direction in new formulation development has
involved the use of lower concentrations of active
agents with the goal of reducing side effects while
optimizing therapeutic effects. Consider 2.5% BPO in
combination with clindamycin (Acanya Gel, Coria
Laboratories), an alternative to the 5% BPO products
on the market. In vitro assessments showed compar-
able bioavailability of BPO from both formulations but
with a 33 percent reduction in irritation in the 2.5%
BPO group controlled to 5% BPO.14 To further opti-
mize tolerability, the vehicle for the BPO 2.5%/clin-
damycin formulation contains emollient ingredients to
reduce local cutaneous irritation.

Another low-concentration formulation offers
micronized tretinoin particles in a 0.05% controlled
release formulation (Atralin Gel, Coria). The moisturiz-
ing hydrogel vehicle contains soluble collagen, sodium
hyaluronate, and glycerin. The delayed release mecha-
nism enhances penetration and uptake into follicle
through sebum, allowing for once-daily application.15

Alternatively, a novel benzoyl peroxide foam for-
mulation offers a higher concentration than a similar
existing agent, but uses an alternative application regi-
men and vehicle features to optimize tolerability.

Benzoyl peroxide 9.8% foam (BenzE Foam Ultra,
Onset/PreCision) was developed for short-contact
application for the treatment of acne on the trunk.
The emollient foam is applied to the dry trunk and left
in place for two minutes before being rinsed off. In a
two-week study involving 20 patients 18 years of age
or older, daily application according to this protocol produced a 98.3 percent reduction in P. acnes counts.16

Retinoid Stability
Tretinoin has poor stability and is degraded by sunlight and oxidizing agents like benzoyl peroxide, therefore, patient must apply the retinoid at night and never in conjunction with other topical medications. That long-standing admonition may not necessarily be accurate, as evidence shows that the formulation of tretinoin affects its stability. In vitro studies show that tretinoin microsphere gel 0.04% (Retin A Micro, OrthoDermatologics) is stable in the presence of BPO and light.17 Additionally, the novel tretinoin 0.05% aqueous gel has also been shown in vitro to be stable in combination with BPO.18 After seven hours of exposure to BPO, no degradation or oxidation of tretinoin was observed.

In vivo evidence shows that application of tretinoin gel microsphere 0.04% to the face after washing with BPO 5% cleanser each evening was no less effective than washing with the BPO cleanser in the morning and applying tretinoin in the evening.19 The 12-week study, (n=247) found similar tolerability for the two regimens, suggesting that the evening only regimen may be an effective and well-tolerated, patient-friendly alternative to the twice-a-day approach.

Tretinoin has also been formulated with clindamycin in fixed combination products with no apparent detrimental effect on the efficacy of tretinoin. Clindamycin phosphate 1.2% and tretinoin 0.025% is available in a foam20 (Veltin, Stiefel/GSK) and gel21 (Ziana, Medicis) formulation. In addition to the differences in the vehicle base, each formulation provides a different mechanism of release of tretinoin. No head-to-head studies have been performed.

A second-generation retinoid, adapalene is stable in the presence of BPO and the two are now available in a single fixed combination gel (adapalene 0.1%/benzoyl peroxide 2.5%, EpiDuo, Galderma). The formulation provided a significant reduction in total, inflammatory, and non-inflammatory lesions in a trial in subjects ages 12 to 17.22 In an analysis of treatment effectiveness and tolerability based on skin type, there was no statistically significant differences in dryness, scaling, and stinging/burning between subjects in the skin type I to III group compared to the type IV to VI group.23 A statistically significantly lower rate or erythema observed among patients with darker skin types may be related to difficulty of assessment.

Dr. Zeichner has served as an advisor, investigator, or consultant for Beiersdorf, Coria, Galderma, Medicus, PharmaDerm and Procter and Gamble.

Joshua A. Zeichner, MD is Director of Cosmetic and Clinical Research at The M ount Sinai School of Medicine and Chief of D ermatology at North General Hospital in New York City.

4. DOH Hawai Dermatology Seminar. March 2011. Dr. R Rox Anderson
16. Legden, I. Poster presented at the Fall Clinical Dermatology Conference. Las Vegas, NV. October 2010.