Light-Emitting Diodes in Dermatology: A Systematic Review of Randomized Controlled Trials

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Objective: In dermatology, patient and physician adoption of light-emitting diode (LED) medical technology continues to grow as research indicates that LEDs may be used to treat skin conditions. The goal of this systematic review is to critically analyze published randomized controlled trials (RCTs) and provide evidence-based recommendations on the therapeutic uses of LEDs in dermatology based on published efficacy and safety data.
Methods: A systematic review of the published literature on the use of LED treatments for skin conditions was performed on September 13th 2017.
Results: Thirty-one original RCTs were suitable for review.
Conclusions: LEDs represent an emerging modality to alter skin biology and change the paradigm of managing skin conditions. Acne vulgaris, herpes simplex and zoster, and acute wound healing received grade of recommendation B. Other skin conditions received grade of recommendation C or D. Limitations of some studies include small patient sample sizes ($n < 20$), absent blinding, no sham placebo, and varied treatment parameters. Due to few incidences of adverse events, affordability, and encouraging clinical results, we recommend that physicians use LEDs in clinical practice and researchers continue to explore the use of LEDs to treat skin conditions. Lasers Surg. Med. © 2018 The Authors. *Lasers in Surgery and Medicine* Published by Wiley Periodicals, Inc.

Key words: light-emitting diode; phototherapy; photobiomodulation; skin therapy

INTRODUCTION

In dermatology, patient and physician adoption of light-emitting diode (LED) medical technology continues to grow as research indicates that LEDs may be used to treat skin conditions. This increased level of interest is evidenced by a doubling of the number of articles published and PubMed indexed on LEDs per year since 2010 (Fig. 1). LEDs are combinable with systemic and topical therapies and may be clinically advantageous due to efficacy, excellent safety of non-ionizing wavelengths, low cost, ease of home use by patients, and portability.

LEDs utilize high-efficiency semiconductors to produce non-coherent, non-collimated light in the ultraviolet (UV), visible, and near-infrared ranges of the electromagnetic spectrum (approximately 255–1300 nm) [1]. LEDs may treat skin conditions by altering intrinsic cellular activity according to the principles of photobiomodulation [1]. Chromophores in the skin, such as mitochondrial cytochrome C, endogenous protoporphyrins, and melanin, absorb photons, and cause downstream alterations in skin biophysiology that can manifest as changes in cellular proliferation, differentiation, migration, inflammation, or collagen production [2–4]. When comparing LED therapy, the following descriptive treatment parameters are commonly used: (i) the wavelength or color of light; (ii) the fluence or the amount of energy received per unit of skin surface area (unit: J/cm^2); (iii) the power density or energy delivered per surface area of skin

Abbreviations: CO_2, Carbon dioxide; ER:YAG, Erbium-doped yttrium aluminum garnet; FDA, Federal Drug Administration; IPL, Intense pulsed light; HSV, Herpes simplex virus; HZV, Herpes zoster virus; LED, Light-emitting diode; LED-BL, Light-emitting diode blue light; LED-nIR, Light-emitting diode near infrared; LED-RL, Light-emitting diode red light; LED-WL, Light-emitting diode white light; LED-YL, Light-emitting diode yellow light; PDT, Photodynamic therapy; RCT, Randomized Controlled Trial; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; UV, Ultraviolet; WHO, World Health Organization

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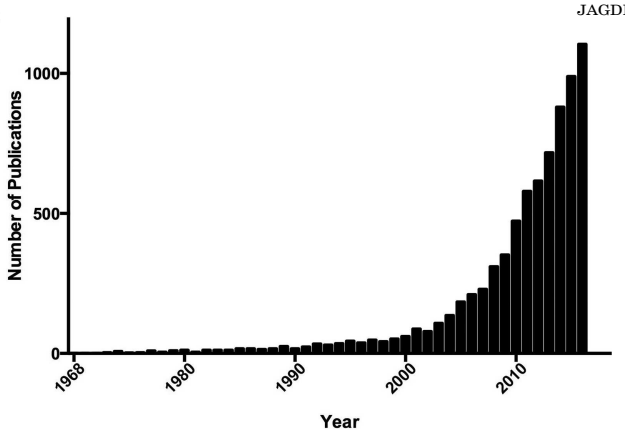

Fig. 1. PubMed cited articles on light-emitting diodes (1968–2016). The number of PubMed indexed articles on light-emitting diodes by publication year (1968–2016). Since 2010, the total number of articles published on light-emitting diodes per year has more than doubled.

(W/cm^2); (iv) treatment period (Seconds); and (v) duty cycle or fraction of treatment length in which light is delivered (expressed as a percentage of treatment period). Each wavelength has unique biophysiological properties due to differences in chromophore targets and how deeply each wavelength penetrates the skin [2]. The relationship between power density, session length, and fluence can be described using this general equation:

$$\text{Power density } (W/cm^2) \times \text{time (seconds)} = \text{fluence } (J/cm^2)$$

The goal of this systematic review is to critically analyze published randomized controlled trials (RCTs) and provide evidence-based recommendations on the therapeutic uses of LEDs in dermatology based on published efficacy and safety data.

METHODS

We performed a search strategy according to *Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA)* protocol on September 13th, 2017. The bibliographies of included publications were checked for additional relevant articles that were not identified in the database search. Each article was independently reviewed by two of the authors. We included published RCTs that used LEDs therapeutically for skin conditions. We excluded articles pertaining to UV light as its therapeutic effects and mechanism of action have been well studied. We excluded studies that lacked an LED-only treatment arm when other photoactive drugs, photosensitizers, lasers, and light-based devices were used. Reviews, conference abstracts, presentations, basic science manuscripts, animal studies, and non-English articles were excluded. A research librarian assisted with the systematic search and the accuracy and completeness of included and excluded articles (Fig. 2).

RESULTS

Our systematic search identified 4,542 articles. After screening titles, abstracts, and full text articles, 31 original

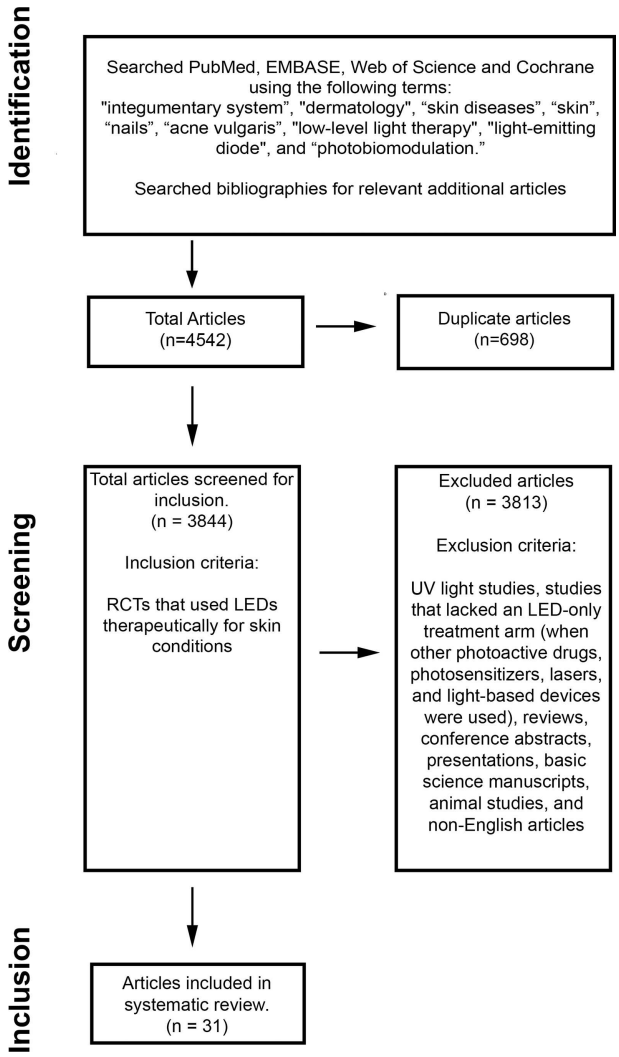

Fig. 2. PRISMA search strategy. Search strategy according to preferred reporting items for systematic Reviews and meta-analysis (PRISMA) protocol.

RCTs using LED blue light (LED-BL), LED red light (LED-RL), LED near-infrared light (LED-nIR) and/or yellow light (LED-YL) were suitable for review: acne vulgaris (8), herpes simplex and zoster [HSV, HZV] (3), skin rejuvenation (6), acute wound healing (5), psoriasis (3), atopic dermatitis (1), chronic wound healing (2), oral mucositis (1), radiation dermatitis (1), and thigh cellulite reduction (1) (Table 1). Grades of recommendation were assigned based on the *Oxford Centre for Evidence-based Medicine—Levels of Evidence* [5]. Table 1 provides a detailed summary of the identified studies and highlights the grades of recommendation, study designs, treatment parameters, results, and adverse events.

CHARACTERISTICS OF LED DEVICES

Among the reviewed studies, there were greater than 20 different LED devices used. A majority of reviewed studies used FDA-cleared or commercially available LED

TABLE 1. RCTs Using Light-Emitting Diodes

Author	Total # of Patients/Drop-Out	Study Design and Biases	Follow-Up	Primary Outcome	Treatment Parameters	Treatment Regimen	Results	Adverse Events
FDA-cleared LED treatments of skin conditions								
Acne vulgaris (8)—Grade of recommendation: B								
Ash et al. [6]	41/5	Rater-blinded, no placebo	12-week	Lesion count	LED-BL (414-nm, 17.6 J/cm^2)*	Every other day for 8 weeks	50.08% decrease	None reported
					No treatment		2.45% increase	
Gold et al. [7]	30/0	Placebo-controlled, split-face	10-day or until resolution	Lesion size	LED-BL (414-nm)*	Four treatments over 2 days	Lesion size—76% decrease Clearance—37%	None reported
					Sham placebo		Lesion size—41% decrease Clearance—10%	
Kwon et al. [8]	35/3	Double-blind, placebo-controlled	12-week	Lesion count	LED-BL (420-nm, 6.1 mW/cm^2, 0.91 J/cm^2) and LED-RL (660-nm, 8.1 mW/cm^2 1.22 J/cm^2) for 2.5 minutes (100% duty cycle)	Twice daily for 4 weeks	Inflammatory lesions—77% decrease Non-inflammatory lesions—54% decrease	Mild dryness, erythema, and desquamation
					Sham placebo		No significant change from baseline	
Liu et al. [9]	20/0	Rater-blinded, no placebo	8-week	Inflammatory lesion count	LED-BL (405-nm, 6.0 mW/cm^2, 7.2 J/cm^2) for 20 minutes. Five regions of face received 20% each of total irradiation	Twice weekly for 4 weeks	71.4% decrease	Skin dryness
					LED-RL (630-nm, 9.6 mW/cm^2, 11.52 J/cm^2) for 20 minites. Five regions of face received 20% each of total irradiation		19.5% decrease	
Liu et al. [10]	150/0	Split-face, no placebo, no blinding	4-month	Sessions till 90% clearance of inflammatory lesions	5% ALA PDT (633-nm, 105 mW/cm^2, 126 J/cm^2) for 20 minutes	Weekly until 90% clearance	3 ± 1.52 sessions	PDT: Pain, erythema, and edema LED and IPL: Minimal erythema and stinging
					IPL (420-nm, 11-15 J/cm^2, 30-40 ms pulses)		6 ± 2.15 sessions	

(*Continued*)

TABLE 1. (*Continued*)

Author	Total # of Patients/Drop-Out	Study Design and Biases	Follow-Up	Primary Outcome	Treatment Parameters	Treatment Regimen	Results	Adverse Events
					LED-RL (633-nm, 105 mW/cm^2, 126 J/cm^2, 50% duty cycle) and LED-BL (415-nm, 40 mW/cm^2, 48 J/cm^2, 50% duty cycle) for 40 minutes	Twice weekly until 90% clearance	9 ± 3.34 sessions	
Na et al. [11]	30/2	Split-face, rater-blinded, no placebo	16-week	Lesion count	LED-RL (635-670-nm; 6 mW/cm^2, 5.4 J/cm^2, 100% duty cycle) for 15 minutes	Twice a day for 8 weeks	Inflammatory lesions—66% decrease Non-inflammatory lesions—59% decrease	Burning sensation
					No treatment		Inflammatory lesions—74% increase Non-inflammatory lesions—3% increase	
Nestor et al. [12]	105/13	Double-blinded, no placebo, missing control groups	12-week	Lesion count	LED-BL (445-nm) and LED-RL (630-nm)*	N/A	Inflammatory lesions—24.4% decrease Non-inflammatory lesions—19.5% decrease	No adverse events
					LED-BL and LED-RL and 1% salicylic acid/retinol*		Inflammatory lesions—22.7% decrease Non-inflammatory lesions—4.8% decrease	
					Topical benzoyl peroxide		Inflammatory lesions—17.2% decrease Non-inflammatory lesions—6.3% decrease	
Sami et al. [13]	45/0	Split-face, rater-blinded, no placebo	1-month following last treatment	Sessions till 90% clearance of inflammatory lesions	PDL (595-nm, 6-8 J/cm^2, 40 ms pulse, 75% duty cycle)	Weekly until 90% clearance	4.1 ± 1.39 sessions	PDL: Mild purpura and PIH LED: No adverse events IPL: Slight stinging and erythema
					IPL (550-1200-nm, 22 J/cm^2, 30 ms pulses)		6.0 ± 2.05 sessions	

(*Continued*)

TABLE 1. (*Continued*)

Author	Total # of Patients/Drop-Out	Study Design and Biases	Follow-Up	Primary Outcome	Treatment Parameters	Treatment Regimen	Results	Adverse Events
					LED-RL (623-nm, 40 mW/cm^2, 48 J/cm^2, 50% duty cycle) and LED-BL (470-nm, 10 mW/cm^2,12 J/cm^2, 50% duty cycle) for 20 minutes	Twice weekly until 90% clearance	10 ± 3.34 sessions	
Herpes simplex and zoster (3)—Grade of recommendation: B								
Dougal and Lee [14]	87/7	Double-blind, placebo-controlled	16-day	Healing time	LED-nIR (1072-nm) for 3 minutes*	Six times over 2 days	5.9 ± 2.6 days	None reported
					Sham Placebo		7.5 ± 3.0 days	
Hargate [15]	32/5	Double-blind, placebo-controlled, self-reported	12-day	Healing time	LED-nIR (1072-nm)*	Six times over 2 days	6.3 ± 2.99 days	No adverse events
					Sham Placebo		9.4 ± 4.58 days	
Park et al. [16]	28/0	Rater-blinded, no placebo	20-day	Healing time	LED-nIR (830-nm, 55 mW/cm^2, 33 J/cm^2, 100% duty cycle) for 10 minutes and oral famciclovir	LED-nIR on days 0, 4, 7, and 10	13.14 ± 2.34 days	No adverse events
					oral famciclovir		15.92 ± 2.55 days	
Skin rejuvenation (6)—Grade of recommendation: C								
Bhat et al. [17]	23/1	Split-face, rater-blinded, no placebo	12-week	Elasticity and hydration	LED-RL (630-nm, 80 mW/cm^2, 96 J/cm^2, 100% duty cycle) for 20 minutes	Three times a week for 3 weeks	No difference between LED-RL and control side	None reported
					No treatment			
Lee et al. [18]	112/36	Split-face, double-blinded, placebo-controlled	16-week	Wrinkles and elasticity	LED-RL (633-nm, 126 J/cm^2, 55 mW/cm^2, 100% duty cycle) for 20 minutes	Twice weekly for 4 weeks	Wrinkles: 26% improvement, elasticity: 14% improvement	No adverse events
					LED-nIR (830-nm, 55 mW/cm^2, 66 J/cm^2, 100% duty cycle) for 20 minutes		Wrinkles: 33% improvement, elasticity: 19% improvement	
					LED-RL and LED-nIR		Wrinkles: 36% improvement, elasticity: 16% improvement	
					Sham Placebo		Wrinkles: No difference, elasticity: no difference	

(*Continued*)

TABLE 1. (*Continued*)

Author	Total # of Patients/Drop-Out	Study Design and Biases	Follow-Up	Primary Outcome	Treatment Parameters	Treatment Regimen	Results	Adverse Events
Miglardi et al. [19]	30/0	Patient rated outcomes, no blinding, no placebo	2-month after last treatment	Patient satisfaction	LED-RL (633-nm, 50% duty cycle) and LED-nIR (880-nm, 50% duty cycle) for 1.17 minutes*	Every 5 days for 40 days	100% satisfaction	No adverse events
					RF	Every 10 days for 50 days	100% satisfaction	
					LED-RL, LED-nIR, and RF*	1 RF and 2 LED treatments every 5 days for 45 days	100% satisfaction	
Nam et al. [20]	52/2	Double-blind, no placebo	12-week	Skin roughness and physician assessment	LED-RL (660-nm, 5.17 J/cm^2, 7.5 mW/cm^2, 15% duty cycle) for 11.5 minutes	Daily for 12 weeks	Improvements in 3/5 roughness parameters compared to baseline. No difference in physician assessment	Ocular symptoms
					LED-WL (411-777-nm, 7.5 mW/cm^2, 15% duty cycle) for 11.5 minutes		Improvements in 4/5 roughness parameters compared to baseline. No difference in physician assessment	
Nikolis et al. [21]	32/2	Placebo-controlled, single-blind, split-faced	12-week	Total wrinkle score	LED-BL (446-nm, 45 J/cm^2, 150 mW/cm^2, 100% duty cycle) for 5 minutes and chromophore gel	Weekly for 4 weeks	Significant improvement	Edema and erythema
					LED-BL and placebo gel		Significant improvement	
					LED-WL and chromophore gel*		Significant worsening	
					0.1% retinol-based cream		No difference	

(*Continued*)

TABLE 1. (*Continued*)

Author	Total # of Patients/Drop-Out	Study Design and Biases	Follow-Up	Primary Outcome	Treatment Parameters	Treatment Regimen	Results	Adverse Events
Stirling and Haslam [22]	79/1	Double-blind, placebo-controlled, patient rated outcomes.	6-10 week	Patient assessment	LED-nIR (1072-nm) for 3 minutes*	Daily for 8–10 weeks	52% reported improvement	No adverse events
					Sham placebo		20% reported improvement	
Non-FDA cleared LED treatments of skin conditions								
Acute wound healing (4)—Grade of recommendation: B								
Alster and Wanitphakdeedecha [23]	20/0	Split-face, rater-blinded, no placebo	96-hour	Erythema	LED-YL (590-nm, 0.1 J/cm^2, 2.86 mW/cm^2) for 35 seconds following erbium-doped fiber laser	Once following laser treatment	At 24 hours less erythema in 20/20 patients in LED-YL treatment group. At 48 hours, less erythema in 6/20 patients. No difference at 96-hour follow-up	None reported
					No treatment following erbium-doped fiber laser			
Bay et al. [27]	20/0	Split-body, double-blind	11-day	Physician assessment, erythema and hyperpigmentation	LED-nIR (830-nm, 65 J/cm^2, 109 mW/cm^2) and LED-YL (595-nm, 0.13 J/cm^2, 0.19 mW/cm^2) for 11 minutes following CO_2 laser assisted red light PDT. Unclear duty cycle for LED-YL and LED-nIR	Daily for 5 days starting one day before CO_2 assisted PDT	No difference in physician assessment, erythema, or hyperpigmentation	None reported
					LED-YL (595-nm, 0.13 J/cm^2, 0.19 mW/cm^2) for 11 minutes following CO_2 laser assisted red light PDT			
Chaves et al. [26]	16/6	Double-blind, placebo-controlled, small population (< 20)	4-week	Sessions to heal and pain	LED-nIR (860-nm, 4 J/cm^2, 50 mW/cm^2, 50% duty cycle) for 79 seconds	Twice weekly for 4 weeks	2-4 sessions, clinically significant reduction in pain following 6 out of 8 treatment sessions. 5-8 sessions, no change in pain after sessions	No adverse events
					Sham placebo			

(*Continued*)

TABLE 1. (*Continued*)

Author	Total # of Patients/Drop-Out	Study Design and Biases	Follow-Up	Primary Outcome	Treatment Parameters	Treatment Regimen	Results	Adverse Events
Khoury and Goldman [24]	15/0	Split-face, rater-blinded, small patient population (<20), no placebo	1-week	Erythema score	LED-YL (590-nm, 71.4% duty cycle) for 35 seconds following IPL (16-22 J/cm^2)*	Once following laser treatment and once at 24 hours post treatment	43.3 ± 21.9 erythema score immediately after treatment. 16.0 ± 15.9 after 24 hours. No difference after 1 week	None reported
					No treatment following IPL		52.7 ± 24.6 erythema score immediately after treatment. 20.0 ± 18.5 after 24 hours. No difference after 1 week	
Trelles et al. [25]	28/0	Split-face, rater-blinded, no placebo	6-month	Physician assessment	LED-RL (633-nm, 96 J/cm^2, 80 mW/cm^2, 100% duty cycle) for 20 minutes and LED-nIR (830-nm, 60 J/cm^2, 55 mW/cm^2, 100% duty cycle) following ER: YAG/CO_2 laser	LED-nIR immediately and 72 hours following ER: YAG/CO_2 laser. Then three LED-RL treatments in following 2 weeks	93% efficacy at 3-month follow-up.100% efficacy at 6-month follow-up. 50% increase in healing time	None reported
					No treatment following ER: YAG/CO_2 laser		86% efficacy at 3-month follow-up. 97% efficacy at 6-month follow-up	
Psoriasis (3)—Grade of recommendation: C								
Kleinpenning et al. [28]	27/0	Split-face, double-blind, no placebo	4-week	SUM score	LED-RL (630-nm, 60 J/cm^2, 50 mW/cm^2, 100% duty cycle) for 20 minutes and salicylic acid	LED − 3 times a week for 4 weeks; salicylic acid- daily for 4 weeks	26.7% improvement	Burning sensation and hyperpigmentation
					LED-BL (420-nm, 120 J/cm^2, 50 mW/cm^2, 100% duty cycle) for 20 minutes and salicylic acid		33.9% improvement	
					10% Salicylic acid		39.4% improvement	

(*Continued*)

TABLE 1. (*Continued*)

Author	Total # of Patients/Drop-Out	Study Design and Biases	Follow-Up	Primary Outcome	Treatment Parameters	Treatment Regimen	Results	Adverse Events
Pfaff et al. [29]	47/2	Split-face, double-blind, no placebo	16-week	LPSI	LED-BL (453-nm, 90 J/cm^2, 200 mW/cm^2) for 30 minutes. Duty cycle differed between treatments but is not directly stated*	Daily (5–7 days) for 4 weeks followed by thrice weekly for 8 weeks	-0.92 ± 1.1 LPSI change	Changes in pigmentation
					LED-BL (453-nm, 90 J/cm^2, 100 mW/cm^2) for 30 minutes. Duty cycle differed between treatments but is not directly stated*		-0.74 ± 1.18 LPSI change	
Weinstbl et al. [30]	40/3	Split face, double-blind, no placebo	6-week	LPSI	LED-BL (420-nm, 90 J/cm^2, 100 mW/cm^2) for 15 minutes	Daily for 4 weeks	Significant improvement compared to untreated plaque at week-4, but not week-6	Hyperpigmentation
					LED-BL (453-nm, 90 J/cm^2,100 mW/cm^2) for 15 minutes		Significant improvement compared to untreated plaque at week-4, but not week-6	
Atopic dermatitis (1)—Grade of recommendation: D								
Keemss et al. [31]	21/1	Split-face, no placebo	6-week	Eczema severity index	LED-BL (453-nm, 90 J/cm^2)* No treatment	Thrice weekly for 4 weeks	30.4% improvement following LED-BL	Mild hyperpigmentation
Chronic wound healing (2)—Grade of recommendation: D								
Frangez et al. [33]	80/1	Double-blind, placebo-controlled	8-week	Circulation and Falanga wound bed score	Diabetic chronic wound: LED-RL (625-nm, 24% of power density and 660-nm, 71% of power density) and LED-nIR (850-nm, 5% of power density). Total 2.4 J/cm^2, 50% duty cycle for 5 minutes. Power density not specified*	Three times weekly for 8 weeks	29% increase in blood flow. Significant improvement in Falanga wound bed score compared to placebo.	None reported

(*Continued*)

TABLE 1. (*Continued*)

Author	Total # of Patients/Drop-Out	Study Design and Biases	Follow-Up	Primary Outcome	Treatment Parameters	Treatment Regimen	Results	Adverse Events
					Diabetic chronic wound: placebo (580-900-nm, 0.72 J/cm^2) for 5 minutes*		11% increase in blood flow	
					Non-diabetic chronic wound: LED-RL and LED-nIR		48% increase in blood flow. Significant improvement in Falanga wound bed score compared to placebo	
					Non-diabetic wound: placebo		12% decrease in blood flow	
Siqueira et al. [32]	17/2	Double-blind, placebo-controlled, small patient population (<20)	30-week	Ulcer surface area and healing rate	LED-RL (625-nm, 4 J/cm^2, 25 mW/cm^2) for 2.67 minutes and Unna boot. In large ulcers (>1 cm^2), five areas of wound received of 4 J/cm^2 for total of 20 J/cm^2 for 800 seconds	Weekly for 30 weeks	Ulcer surface area change 9.8% of baseline (9.8% to 31.2% quartiles). Healing time hazard ratio of 0.89 (95%CI 0.4-1.98)	None reported
					Sham placebo and Unna boot		Ulcer surface area change 112% of baseline (18.7% to 417% quartiles)	
Oral mucositis (1)—Grade of recommendation: D								
Hodgson et al. [35]	80/0	Double-blind, placebo-controlled	2-week	WHO pain assessment scale	LED-RL (670-nm, 4 J/cm^2, 50 mW/cm^2) for 80 s Sham Placebo	Daily for 2 weeks	44% less pain in LED-RL high-risk group compared to sham placebo high-risk group. No difference for low-risk group	None reported
Radiation dermatitis (1)—Grade of recommendation: D								
Fife et al. [38]	33/4	Double-blind, placebo-controlled	6-week	NCI grading	LED-YL (590-nm, 71.4% duty cycle) for 35 seconds* Sham Placebo (machine not turned on)	Before and after each radiation session and seven additional	No difference in NCI grades between groups	No adverse events

(*Continued*)

TABLE 1. (*Continued*)

Author	Total # of Patients/Drop-Out	Study Design and Biases	Follow-Up	Primary Outcome	Treatment Parameters	Treatment Regimen	Results	Adverse Events
						treatments for 2 weeks		
Thigh cellulite reduction (1)—Grade of recommendation: D								
Sasaki et al. [39]	9/0	Split-face, double-blind, small patient population (<20)	18-month	Thigh cellulite grade	LED-RL (660-nm) and LED-nIR (950-nm) and placebo gel* LED-RL and LED-nIR and phosphatidylcholine gel*	Twice weekly for 12 weeks	0/9 thighs improved 8/9 thighs improved at 3-month follow-up. Recurrence in 3/8 thighs	None reported

LED, Light-emitting diode; RL, Red light; BL, Blue light; YL, Yellow light; WL, White light; nIR, Near infrared; PDT, Photodynamic therapy; IPL, Intense pulsed light; RF, Radiofrequency; PDL, Pulsed dye light; ER:YAG, Erbium-doped yttrium aluminum garnet; CO_2, Carbon dioxide; WHO, World Health Organization; NCI, National Cancer Institute; LPSI, Local Psoriasis Severity Index; Min, Minimum; Max, Maximum; CI, Confidence interval, PIH, Post-inflammatory Hyperpigmentation; OMI, Oral Mucositis Index.
If LED treatment parameters (ie, fluence, power density, or treatment length) were not included in the original article, an asterisk (*) marks the treatment parameters.

devices (Table 2). LED treatment parameters (wavelength, power density, fluence, and session length) are included in the description of each study and Table 1. If LED treatment parameters were not included in the original article, an asterisk (*) marks the treatment parameters in text. Duty cycle is 100% unless otherwise indicated.

FDA-CLEARED LED TREATMENTS OF SKIN CONDITIONS

Acne Vulgaris—Grade of Recommendation: B

Eight RCTs used LEDs for acne vulgaris (2 LED-BL; 1 LED-RL; 5 LED-BL and LED-RL) [6–13]. One RCT of 41 patients used LED-BL* (414-nm, 17.6 J/cm^2) every other day for 8 weeks and demonstrated a 52% reduction in lesion count compared to no treatment control [6]. In a placebo-controlled RCT of 30 patients, LED-BL* (414-nm) decreased lesion size by 35% after twice-daily treatment for 2 days [7].

In one split-face RCT of twice daily LED-RL (635–670-nm, 6 mW/cm^2, 5.4 J/cm^2,15 minutes) for 8 weeks, there was a 66% and 59% reduction in inflammatory and non-inflammatory lesion count, respectively. However, by 16-week follow-up, 21 out of 22 patients complained of acne recurrence [11]. One RCT of 20 patients compared twice weekly LED-RL (630-nm, 9.6 mW/cm^2, 11.52 J/cm^2, 20 minutes) to LED-BL (405-nm, 6.0 mW/cm^2, 7.2 J/cm^2, 20 minutes) for 4 weeks in which five regions of the face received 20% of total irradiation each; LED-BL reduced lesion count by 71.4% compared to 19.5% in LED-RL [9].

Two RCTs of 105 and 35 patients used combination LED-BL* (445-nm or 420-nm, 6.1 mW/cm^2, 0.91 J/cm^2, 2.5 minutes) and LED-RL* (630-nm or 660-nm, 8.1 mW/cm^2 1.22 J/cm^2, 2.5 minutes). LED-BL and LED-RL reduced inflammatory lesion count (24–77%) compared to placebo control (0%) or topical benzoyl peroxide treatment (17.2%) groups at 12 week follow-up [8,12]. Two RCTs of 150 and 45 patients compared time to achieve 90% clearance with combination twice weekly LED-RL (623-nm, 40 mW/cm^2, 48 J/cm^2, 50% duty cycle, 20 minutes or 633-nm, 105 mW/cm^2, 126 J/cm^2, 50% duty cycle, 40 minutes) and LED-BL (470-nm, 10 mW/cm^2,12 J/cm^2, 50% duty cycle, 20 minutes or 415-nm, 40 mW/cm^2, 48 J/cm^2, 50% duty cycle, 40 minutes) compared to weekly photodynamic therapy (PDT), intense pulse light (IPL) or pulsed dye laser therapy (PDL) [10,13]. All treatments improved acne compared to baseline, but LED-BL and LED-RL required 2–3 times as many sessions to achieve 90% clearance compared to PDL, IPL, and PDT.

Clinical recommendation. We recommend LED-BL or LED-RL with power densities of 6–40 mW/cm^2 or 8–100 mW/cm^2, respectively, for 20 minutes to safely reduce inflammation and lesion count. Treatments may be offered twice weekly for 4–8 weeks for best efficacy. The reviewed studies used heterogeneous treatment parameters, and it is difficult to state the exact optimal power density or fluence. We identified more than 10 case series demonstrating similar trends, which support our recommendation. PDL, PDT, and IPL required fewer treatment

TABLE 2. FDA-Cleared LED Treatments of Skin Conditions

Device Wavelength	Device Names (Manufacturer)	Skin Indication
LED-BL	Tanda Zap (Syneron), Illumask (La Lumiere/Neutrogena/Johnson & Johnson), Omnilux Blue (Photo Therapeutics)	Mild to moderate acne
LED-RL	Young Again (Espansione), Omnilux Revive (Photo Therapeutics)	Acne vulgaris, vascular/pigmented lesions, and rhytides
LED-YL	Gentlewaves (Light Bioscience)	Rhytides
LED-nIR	Young Again (Espansione), Virtulite cold sore machine (Virtulite)	Rhytides and facial herpes simplex

sessions to achieve clearance, but LEDs may be safe for home use. LEDs may be especially beneficial for pregnant women with acne vulgaris as retinoid treatments are pregnancy class C (ie, animal studies have shown harm, but there are not enough high quality studies in humans to judge safety).

Herpes Simplex and Zoster—Grade of Recommendation: B

Three RCTs used LED-nIR for the treatment of recurrent facial HSV or HZV [14–16]. In two placebo-controlled, double-blind RCTs of 87 and 32 patients, six treatments of LED-nIR* (1072-nm) over 2 days resulted in a 2–3 days reduction in re-epithelialization time in patients with labial HSV infections by 12–16 days follow-up [14,15]. In a RCT of 28 patients with HZV, LED-nIR (830-nm, 55 mW/cm^2, 33 J/cm^2,10 minutes) for four treatments over 10 days with oral famciclovir resulted in reduced healing time, less atrophic scarring, and fewer incidences of post-inflammatory hyperpigmentation compared to famciclovir alone treatment [16].

Clinical recommendation. LED-nIR treatment significantly and consistently reduced healing time by at least 2 days in patients with HSV and HZV. Two of these studies did not describe treatment parameters used and it is therefore difficult to translate the findings to clinical practice. Thrice daily LED-nIR for 3 days may be a useful at-home adjunct with standard-of-care oral anti-viral medications to enhance recovery. Based on the results of one of the RCTs the following treatment parameters may be safe and effective: 830-nm, 55 mW/cm^2, 33 J/cm^2 for 10 minutes.

Skin Rejuvenation—Grade of Recommendation: C

Six RCTs used LEDs for skin rejuvenation (2 LED-RL; 1 LED-nIR; 1 LED-BL; 2 LED-RL and LED-nIR) [17–22]. In a RCT of 23 patients, LED-RL (630-nm, 80 mW/cm^2, 96 J/cm^2, 20 minutes) did not significantly improve skin elasticity or hydration (assessed using cutometers and corneometers) compared to untreated controls after thrice daily treatments for 3 weeks [17]. In a different RCT of 52 patients, LED-RL (660-nm, 5.17 J/cm^2, 7.5 mW/cm^2, 15% duty cycle, 11.5 minutes) or LED white light (LED-WL; 411–777-nm, 7.5 mW/cm^2, 15% duty cycle, 11.5 minutes) improved wrinkles in three out of five parameters using digital analysis but there were no changes in physician assessment [20]. In a double-blind, placebo-controlled RCT of 79 patients, there was a 32% improvement in skin texture following daily LED-nIR* (1072-nm, 3 minutes) treatment for 8–10 weeks by patient self-assessment. In a RCT of 32 patients, LED-BL (446-nm, 45 J/cm^2, 150 mW/cm^2, 5 minutes) and a placebo gel improved wrinkles compared to a 0.1% retinol-based cream after four weekly treatments [21].

One placebo-controlled RCT of 112 patients found that LED-RL (633-nm, 126 J/cm^2, 55 mW/cm^2, 20 minutes), LED-nIR (830-nm, 55 mW/cm^2, 66 J/cm^2, 20 minutes), or combination LED-RL (50% duty cycle) and LED-nIR (50% duty cycle) twice weekly for 4 weeks improved wrinkles by 26%, 33%, and 36%, respectively.[18] In another RCT, 30 patients were satisfied when receiving LED-RL* (633-nm, 50% duty cycle, 1.17 minutes) and LED-nIR* (880-nm, 50% duty cycle, 1.17 minutes), radiofrequency, or combination (LED with radiofrequency) treatments after 5–27 treatments over 40–50 days [19].

Clinical recommendation. Clinical evidence indicates that daily LED-nIR with LED-RL for 8–10 weeks has the best efficacy in improving rhytides. There is a high level of variability in treatment parameters and future studies may seek to optimize power densities, fluences, and session lengths. Several researchers have used LED-YL with success in case series, but our search did not reveal any RCTs studying LED-YL for skin rejuvenation [4]. Therapies for skin rejuvenation often have gradual results, and 6-month or longer follow-up may be required to assess the efficacy of LEDs for long-term skin rejuvenation.

NON-FDA CLEARED LED TREATMENTS OF SKIN CONDITIONS

Acute Wound Healing—Grade of Recommendation: B

Five RCTs used LEDs (1 LED-nIR; 2 LED-YL; 1 LED-RL and LED-nIR; 1 LED-nIR and LED-YL) for enhanced wound healing and recovery following acute trauma or laser skin procedures [23–26]. One double-blind, placebo-controlled RCT used twice weekly LED-nIR (860-nm, 4 J/cm^2, 50 mW/cm^2, 50% duty cycle; 1.31 minutes) for 4 weeks to treat nipple trauma in sixteen breastfeeding female patients. There was a reduction in lesion area and pain after LED-nIR therapy [26]. Two split-face RCTs used LED-YL* (590-nm, 0.1 J/cm^2, 2.86 mW/cm^2; 35 seconds or 590-nm, 71.4% duty cycle) to improve wound healing and

erythema immediately following erbium-doped laser or IPL therapy for photodamaged skin [23,24]. LED-YL improved erythema in 20 out of 20 patients and there was a physician-evaluated reduction in erythema at 24 hours follow-up [23,24]. In a split-face RCT of 28 female patients treated with ER:YAG or CO_2 laser for photodamaged skin, healing time was 50% faster on the combination LED-RL (633-nm, 96 J/cm^2, 80 mW/cm^2, 50% duty cycle, 20 minutes) and LED-nIR (830-nm, 60 J/cm^2, 55 mW/cm^2, 50% duty cycle, 20 minutes) treated side compared to no treatment after 15 treatments over 3 weeks [25]. One double-blind, split-body RCT compared combined LED-nIR (830-nm, 65 J/cm^2, 109 mW/cm^2, unclear duty cycle, 11 minutes) and LED-YL (595-nm, 0.13 J/cm^2, 0.19 mW/cm^2, 11 minutes) to LED-YL alone for reduced erythema and pigmentation following CO_2 assisted red light PDT [27]. There was no significant difference between LED-nIR and LED-YL compared the LED-YL in physician assessment, erythema, or hyperpigmentation. The authors considered "ultra-low fluence" LED-YL as a "placebo," but low fluence and power density LED-YL may improve wound healing. As a result, this study is lacking a true placebo.

Clinical recommendation. Daily LED-YL (590-nm) or LED-nIR (830-nm) until wound resolution may reduce healing time and erythema in acute wound healing processes of different etiologies. For LED-YL, data indicates that one to 2 minutes of 5 mW/cm^2 LED-YL help acute wound healing process. Higher fluences (5–40 J/cm^2), power densities (~50 mW/cm^2), and session length (~20 minutes) may be required for LED-nIR treatments. The included RCTs have short follow-up (7 days or less) and future studies using LED-YL or LED-nIR may assess patients at later time points to determine reduction of scarring following LED therapy.

Psoriasis—Grade of Recommendation: C

Three double-blind, split-body RCTs used LEDs (2 LED-BL; 1 LED-BL and LED-RL) to manage psoriasis [28–30]. Two split-body RCTs compared daily LED-BL of different wavelengths (420-nm or 453-nm), irradiances (200 or 100 mW/cm^2), and duty cycles (100% or not specified)* for 4 weeks, and both studies showed a significant improvement in local psoriasis severity index compared to the contralateral untreated control plaques [29,30]. In both studies fluence was consistent at 90 J/cm^2. Lesions recurred in one of these studies after treatment cessation. One split-body RCT of 27 patients found that thrice weekly LED-RL (630-nm, 60 J/cm^2, 50 mW/cm^2, 20 minutes) and LED-BL (420-nm, 120 J/cm^2, 50 mW/cm^2, 20 minutes) for 4 weeks reduced patient psoriatic plaque erythema and induration by 26.7% and 33.9%, respectively, but not significantly compared to daily salicylic acid in petroleum after 4 weeks [28] Salicylic acid had the greatest effect on plaque desquamation, while LED-RL and LED-BL decreased erythema.

Clinical recommendation. LED-BL (at least 90 J/cm^2, 50 mW/cm, 20 minutes) may be effective for the treatment of psoriasis with best results achieved with daily treatments. The reviewed studies do not provide enough evidence to recommend whether 50, 100, or 200 mW/cm^2 power densities are most effective. According to clinical evidence, the treatment parameters and regimens studied have greatest effect on the inflammatory component of psoriasis and not the hyperproliferative component of the psoriatic plaques. Lesions recurred following LED-BL treatment cessation in one study, a common issue associated with discontinuation of psoriasis treatment.

Atopic Dermatitis—Grade of Recommendation: D

In a split-face RCT of 21 patients, thrice weekly LED-BL (453-nm, 90 J/cm^2)* for 4 weeks improved erythema, edema, lichenification, and crusts by 30.4%, according to the eczema severity index [31].

Clinical recommendation. LED-BL may improve atopic dermatitis. There is limited evidence to make clinical recommendations and additional RCTs are required. We did not identify any non-RCTs studying LEDs for atopic dermatitis.

Chronic Wound Healing—Grade of Recommendation: D

Two RCTs used LEDs (1 LED-RL; 1 LED-RL and LED-nIR) for chronic wounds [32,33]. One RCT compared LED-RL (625-nm, 4–20 J/cm^2, 25 mW/cm^2 2.67–13.33 minutes) and Unna boot. plus Unna boot to Unna boot alone in patients with chronic venous ulcers [32]. Overall healing time was not improved in the LED treatment group. One double-blind RCT used combination LED-RL* (625-nm, 12% duty cycle and 660-nm, 35.1% duty) and LED-nIR (850-nm, 2.5% of power density) for 5 minutes for a total fluence of 2.4 J/cm^2 to treat 80 patients with diabetic or non-diabetic chronic ulcer. Wound healing and blood flow improved by 18–60% compared to LED-WL* (580–900-nm, 0.72 J/cm^2, 5 minutes) [33].

Clinical recommendation. There is insufficient evidence to recommend LEDs for chronic wounds. We have previously published a review of photobiomodulation therapy of diabetic ulcers, and evidence from case reports and case series show that light therapy may provide benefit [34]. Differences in treatment regimen and study sample size powering may be responsible for the contradictory results. Researchers may consider reevaluating successful treatment parameters in larger studies [33].

Oral Mucositis—Grade of Recommendation: D

In one double-blind RCT of 80 bone-marrow transplant patients, daily LED-RL (LED-RL (670-nm, 4 J/cm^2, 50 mW/cm^2,1.33 minutes) for 2 weeks did not alter the onset of oral mucositis compared to placebo [35]. One subset of patients, those with regular risk for developing oral mucositis, reported 44% less pain using the World Health Organization (WHO) pain assessment scale following LED-RL therapy [35].

Clinical recommendation. There is insufficient evidence to suggest that LEDs improve or prevent oral

mucositis. RCTs, expert opinion, and anecdotal evidence supports the use of low-level laser and light-based therapy over LEDs for patients at high risk for oral mucositis [36].

Radiation Dermatitis—Grade of Recommendation: D

One double-blind, placebo-controlled RCT examined the use of LED-YL* (590-nm, 71.4% duty cycle, 35 seconds) treatment for 2 weeks to prevent radiation dermatitis in 33 breast cancer patients [37,38]. LED-YL was applied before and after each radiation session and seven additional times in a 2 week regimen. LED-YL did not alter the onset or severity of dermatitis as assessed by the National Cancer Institute grading system.

Clinical recommendation. There is insufficient evidence to recommend LEDs for radiation dermatitis. A previous cohort study with the same LED-YL treatment regimen showed decreased onset of radiation dermatitis, but this RCT was unable to replicate those results [37]. Larger sample sizes may be needed to demonstrate benefit.

Thigh Cellulite Reduction—Grade of Recommendation: D

In a double-blind, split-face RCT of nine patients, twice weekly LED-RL* (660-nm) and LED-nIR* (950-nm) for 12 weeks did not improve cellulite with a placebo gel [39]. Combination phosphatidylcholine gel, LED-RL, and LED-nIR reduced cellulite in eight patients.

Clinical recommendation. We do not recommend LEDs to reduce thigh cellulite, as LED alone did not result in improvement in thigh cellulite reduction.

DISCUSSION

Based upon our systematic review of 31 RCTs, we provide evidence based suggested treatment parameters and regimens for LED therapy for skin conditions which dermatologists may tailor to meet patient needs. Scientific evidence exists that supports that LEDs may improve outcomes in acne vulgaris, HSV, HZV, and acute wound healing. LED treatments were safe and well tolerated by patients. Adverse events were mild and included pigment changes, dryness, erythema, desquamation, and stinging. No severe adverse events were reported. There is a theoretical risk of malignancy and photoaging from LED-BL as the wavelengths emitted by LED-BL devices are near UVA, but based on the reviewed studies with a maximum follow-up of 18 months, there were no reports of carcinogenesis or accelerated photoaging. Outside the scope of this review, LEDs may be used in PDT with topical or systemic medications.

LIMITATIONS

Limitations of some studies include small patient sample sizes ($n < 20$), absent blinding, no sham placebo, and varied treatment parameters which makes it difficult to compare study outcomes. Future studies using LEDs may address the aforementioned limitations through the use of sham placebo and temperature-matched controls to ensure that the results are solely due to photobiomodulatory effects. However, with light-based studies, it is sometimes difficult to blind both provider and patient, and placebo treatments are also challenging. There are several key factors that determine clinical outcomes, and all are important: peak wavelength and distribution range, power density at treatment site, treatment time period, total fluence, and treatment regimen. Although most studies used commercially available LED devices, differences in light output and power densities among manufacturers' devices may contribute to outcome variability. It is possible that some clinical studies that did not achieve desired outcomes are using LEDs at a sub-optimal regimen, wavelength, power density, or fluence for the desired therapeutic effect. For example, studies may have used similar wavelength(s) and fluences, but the power densities may be drastically different. A high power density or low power density light source may be used for different treatment session lengths to achieve the same fluences. Even though fluences will be the same, these differences in power densities may alter the results of a study. Pulsing versus continuous treatments may also be significant to clinical outcomes, but there is not enough data to make a recommendation. In the published literature, actual duty cycles may not necessarily equal device on/off time. Due to the angle of divergence inherent in many of the LEDs, the distance to treatment surface is often critical and the delivered power density may be very different than what is published. Surface area in cm^2 and therefore power density (W/cm^2) may change due to small differences in the distance from the LED to the skin surface. As a result, it is difficult to determine if heterogeneity in treatment parameters changes treatment efficacy. Photobiomodulation tends to have biphasic dose response and LED treatment parameters are often not tailored to specific indications [40]. Low-fluence LED therapies are usually appropriate when cell growth or collagen production is desired, while high-fluence LED therapies may have inhibitory effects [40]. There may be clinical exceptions to this biphasic response. As a result, future RCTs will need to clearly detail treatment parameters and optimize wavelength, fluence, and power density for each skin condition in order to determine the efficacy of LEDs for each skin condition.

CONCLUSION

LEDs represent an emerging modality to alter skin biology and change the paradigm of managing skin conditions. Based on the published evidence, acne vulgaris, HSV, HZV, and acute wound healing received grade of recommendation B. Other skin conditions received grade of recommendation C or D. Due to few adverse events, affordability, and encouraging clinical results, we recommend that physicians use LEDs in clinical practice and researchers continue to explore the use of LEDs to treat skin conditions. As therapeutic LED technology is further translated from a research setting to clinical practice, we anticipate that standardized treatment protocols with

consistent treatment wavelengths, fluences, and regimens for additional dermatologic indications will be established.

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