A Systematic Review of Picosecond Laser in Dermatology: Evidence and Recommendations

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Background and Objectives: The use of picosecond laser in dermatology was originally focused on optimizing the removal of unwanted tattoos. Subsequent advances in this technology have broadened its clinical indications to include treatment of benign pigmented lesions, photodamage, melasma, and scar revision. In this systematic review, evidence-based recommendations are developed for the use of picosecond laser in dermatology.
Study Design/Materials and Methods: A comprehensive search of the English language literature was performed up to and including November 2019. Relevant citations were individually evaluated, synthesized, and categorized based on the Level of Evidence. With the addition of the authors' combined clinical experience, clinical recommendations were developed.
Results: After application of inclusion and exclusion criteria, a total of 77 unique studies were evaluated. Treatment of benign pigmented lesions was associated with level I–IV evidence; rejuvenation was associated with level II evidence; melasma was associated with level II evidence; scar revision was associated with level II–III evidence; tattoo removal was associated with level I evidence.
Conclusion: Picosecond laser is a safe and effective treatment modality for an increasing range of dermatologic indications. Further development of this technology is warranted. Lasers Surg. Med. © 2020 Wiley Periodicals, Inc.

Key words: picosecond laser; photothermolysis; laser-induced optical breakdown; benign pigmented lesions; melasma; scar; photodamage; rejuvenation; systematic review; photomechanical

INTRODUCTION

Since the advent of selective photothermolysis, the importance of laser pulse duration in achieving clinical effects within specific tissue targets has been well-recognized [1]. In general, lasers utilized in dermatologic surgery can be classified as either long-pulsed lasers (with pulse durations in the microsecond to millisecond ranges) or short-pulsed lasers (with pulse durations in the nanosecond to picosecond ranges). Currently available picosecond lasers in dermatology have pulse durations between 300 and 900 picoseconds. Originally designed for tattoo removal, picosecond lasers have since shown efficacy in treating a wide range of cutaneous conditions.

Previous seminal works have established the proposed mechanism of action of picosecond laser [2–4]. Briefly, in the setting of an unfractionated beam, the ultra-rapid temperature changes induced by picosecond pulses generate strong acoustic shockwaves within target chromophores resulting in tensile stresses that exceed the fracture threshold of these targets. This photomechanical or photoacoustic effect is the primary method whereby tattoo ink particles and cellular melanosomes are shattered by picosecond laser irradiation, thus facilitating clearance by macrophages and other phagocytes.

On the contrary, picosecond laser energy can be fractionated via a variety of diffractive or holographic lens arrays. Fractionation allows for higher peak energies to be concentrated within laser microbeams, while sparing adjacent tissue. The tissue effects of fractionated picosecond laser rely on chromophore-assisted ionized plasma formation—a phenomenon that has been termed "laser-induced optical breakdown" [4]. The initiating event is the generation of a seed electron after laser irradiation of tissue. The threshold energy required to generate seed electrons via multiphoton absorption without chromophore assistance has been estimated at 10^{13} W/cm^2—a level that is far too high to safely induce in human skin. However, the addition of absorptive chromophore generates thermal effects that exponentially lowers this threshold [5]. Multiphoton microscopy and other histologic studies have suggested that the predominant chromophore in the skin that contributes to this process is melanin, with hemoglobin also potentially playing a role [6,7]. Immediately following laser irradiation, formalin-fixed histological sections reveal discrete vacuoles left behind by the disappearance of plasma. Beyond the

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boundaries of these vacuoles, no tissue damage is observed. These vacuoles then fill with melanotic and other cellular debris within the first 24 hours before being transeliminated through the epidermis over the next 3–7 days [4]. A more delayed analysis of the skin reveals a neocollagenesis and neoelastinogenesis response, which may be due to the localized thermal effects of superheated plasma and/or a photoacoustic stimulation of cell signaling that propagates deeper into the dermis beyond the depth of acute tissue injury readily detectable on immediate histology [8–10]. A significantly higher heat signature associated with fractionated picosecond laser irradiation as compared with non-fractionated delivery may also contribute to tissue remodeling [11].

In this study, we systematically review and critically analyze the available literature on dermatologic applications of picosecond laser and offer recommendations to optimize its use in daily clinical practice.

METHODS

A comprehensive search of all published literature on the dermatologic applications of picosecond laser was performed up to March 2020. The following combination search terms were utilized as "all fields" queries:

1. Picosecond AND tattoo.
2. Picosecond AND melasma.
3. Picosecond AND rejuvenation.
4. Picosecond AND scar.
5. Picosecond AND pigment.
6. Picosecond AND argyria.
7. Picosecond AND dermatology.
8. Picosecond AND cutaneous.
9. Picosecond AND skin.
10. Picosecond AND nevus.
11. Picosecond AND (lentigo OR lentigines).
12. Picosecond AND (freckles OR ephelides).
13. Picosecond AND (epidermis OR epidermal).
14. Picosecond AND (dermis OR dermal).
15. Picosecond AND trial.

A reference manager program (Endnote X9; Clarivate Analytics, Philadelphia PA) was used to identify and remove duplicate findings. Inclusion and exclusion criteria were then manually applied to the remaining citations. Inclusion criteria were any primary clinical study on the application of picosecond laser within dermatology including case reports, case series, retrospective reviews, prospective open-label trials, comparative clinical trials, randomized controlled trials, and systematic reviews. Exclusion criteria were non-systematic review articles, non-human studies, non-clinical studies, non-English language studies, non-picosecond laser studies, and non-dermatologic studies.

Studies were classified according to specific dermatologic indications and tabulated in a chronological fashion. The Level of Evidence for each indication was then assessed according to modified criteria published by the Oxford Center of Evidence-Based Medicine as previously described (Fig. 1) [12]. It is important to note that these data are derived from heterogenous studies with different grading scales and classification systems utilized. For example, a study that utilizes a 4-point improvement scale with 0 denoting 0–25% improvement would report a 12.5% improvement even if baseline and post-treatment results were identical. This variability impacts interpretation of these data. Therefore, a detailed breakdown of all studies included in this review has been summarized in Data Tables 1–6 and finer scrutiny can be applied by the reader if so desired. Finally, practical "Bottom Line" clinical summary and recommendations were proposed taking into account the evidence-based approach in combination with the authors' collective clinical experience with picosecond laser.

RESULTS

The search strategy yielded a total of 648 citations. Removal of duplicates resulted in 278 that remained. Of these, a further 201 citations were excluded based on non-dermatology/non-picosecond (141), non-English (6), non-human/non-clinical (21), and review articles (35). The remaining 78 citations could be classified into one of the five categories: discrete pigmented lesions, other non-melasma pigmented conditions, rejuvenation, melasma, scar revision, and tattoo removal. These data are summarized in Tables 1–6.

DISCRETE PIGMENTED LESIONS

Picosecond lasers with wavelengths of 532, 755, and 1064 nm have been reported to be safe and effective in the treatment of a wide range of discrete pigmented lesions including solar lentigines, freckles, verrucus epidermal nevus, café au lait macules (CALM), nevus of Ota, and Hori's macules. A total of five case reports/series; five retrospective reviews; three prospective open-label trials; and four split-face/lesion randomized comparison trials involving a cumulative 320 subjects have documented these findings [13–29].

Unwanted solar lentigines are common complaints among patients presenting for cosmetic dermatologic treatment. Similar to the previous generation of nanosecond lasers, picosecond lasers have demonstrated excellent efficacy in the removal of these lesions. When utilizing short-pulsed laser for the treatment of benign pigmented lesions, the recommended clinical endpoint is whitening of the lesion with preservation of normal surrounding skin [90]. In fair-skinned individuals, achieving this endpoint leads to safe and effective removal, typically within 1–2 treatment sessions. However, the use of nanosecond lasers for the treatment of benign lentigines in skin of color has a relatively high risk of PIH, with previous estimates ranging between 25 and 47% [91]. In contrast, recent studies have suggested that the risk of PIH when treating lentigines in skin of color with picosecond lasers is lower. Guss et al. used a 375 picoseconds pulsed 532 nm frequency-doubled Nd:YAG laser to treat 255 discrete lentigines in six patients with type IV skin

Level of Evidence	Types of Studies	Recommendation
1a	• Systematic review of randomized controlled trials (RCTs) with homogeneity • ≥ 2 high quality RCTs[a] (homogenous, consistent results) • ≥ 2 high quality prospective right-left comparison trials (PRLCs)[b] (homogenous, consistent results)	**A**: Strong, consistent level 1 studies
1b	• Individual high quality RCT • Individual high quality PRLC	
2a	• PRLC with control being "no treatment" • Multiple low quality RCTs and/or PRLCs with concordant results	**B**: Moderate, consistent level 2 studies
2b	• Low quality RCT[c] • Low quality PRLC[d] • ≥ 3 placebo-controlled open label trials (OLTs) with concordant results	
2c	• Placebo-controlled OLT	
3a	• OLT with controls being "no treatment"	**C**: Weak, consistent level 3 studies
3b	• ≥ 3 case series (homogeneity, consistent results) • OLT with no controls, patients >10	
3c	• Retrospective uncontrolled observational study	
4a	• Individual case series • OLT with no controls, patients <10	**D**: Very weak, consistent level 4 studies
4b	• Case reports (cumulative patient number ≥ 3) with homogenous patients, treatment and results	
5	• Expert opinion without explicit critical appraisal • Based on physiology, bench research or "first principles"	Inconclusive, no recommendations made

Quality of Study	Criteria
[a] **High quality randomized controlled trial (RCT)**	Placebo-controlled Double blinded (or investigator blinded) Lack of significant unaccounted for drop-out subjects Free of selected reporting Matched treatment and control groups +/- follow-up
[c] **Low quality RCT**	Lack of *high quality controls* Or lack of 2 or more of above criteria Or inadequacy/obscurity in 3 or more of above criteria
[b] **High quality prospective right-left comparison trials (PRLC): each patient receives same treatment and control in split/face body method**	Randomization Placebo-controlled Double-blinded (or investigator-blinded) Lack of significant unaccounted for drop-out subjects Free of selected reporting Matched left and right-sided lesions +/- follow-up
[d] **Low quality PRLC**	Lack of *high quality controls* Or lack of 2 of more of above criteria Or inadequacy/obscurity in 3 or more of above criteria

[*]Modified according to the Oxford Centre of Evidence Based Medicine

Fig. 1 Modified levels of evidence classification.

TABLE 1. Discrete Pigmented Lesions

Author/date	Lesion	*N*	Study type	Skin type	Settings	Results	Complications	Device	Fractionated
Chestnut et al. [13]	Nevus of Ota	3	Case series	IV	755 nm 750 ps 3–4 mm spot 1.59–2.83 J 2–3 treatments	All had improved response compared with 4–10 previous sessions of QSR, AL, and Yag	None	Picosure	No
Chan et al. [14]	Ota, Hori, CALM, Lents, Becker, spilus	13	Retro review	III–IV	755 nm 750 ps 2–4 mm 1.76–4.08 J 1–7 treatment	25–100% resolution in all patients; treatment best for Ota and CALM, less so for Beckers Lents, and Hori	None	Picosure	No
Guss et al. [15]	Lents	6	Case series	III–IV	532 nm 375 ps 4–6 mm spot 0.5–0.8 J 1 treatment	78% with 75–100% clearance	1% worsened	Picoway	No
Jerdan et al. [16]	Nevus of Ota	1	Case report	IV	532 nm 750 ps 6 mm spot 0.5 J 2 treatments	Near-complete resolution; previous treatments with QS and Pico 1064 ineffective	None	Enlighten	No
Artzi et al. [17]	CALM	16	Retro review	II–IV	532 nm 375 ps 4-5 mm spot 0.8–1.6 J 1–4 treatment	15/16 patients had good to excellent response with significant to complete resolution	1 patient had no response to the treatment	Picoway	No
Yu et al. [18]	Hori	33	PRLC	III–IV	PSAL vs. QSAL in split face, randomized trial PSAL: 2–2.5 mm spot 750 ps 4.07–6.37 J QSAL: 70 ns	Efficacy PSAL vs. QSAL: 3.73 vs. 2.4 97% good to excellent vs. 46% 93% satisfied to very satisfied vs. 40% Tolerability PSAL vs. QSAL: Pain—4.47 vs. 5.16 Scabbing (d)—6.72 vs. 7.77	PIH	Picosure vs. Accolade	No

(*Continued*)

TABLE 1. (*Continued*)

Author/date	Lesion	*N*	Study type	Skin type	Settings	Results	Complications	Device	Fractionated
					3 mm spot 6–8 J 3 treatments, 6 months apart	PIH—28% vs. 54%; duration (m): 1.32 vs. 1.74			
Peng et al. [19]	Nevus of Ota	29	Retro review	III–IV	755 nm 750 ps 2–4 mm spot 1.96–6.37 J 1–5 treatments	1 treatment— 28% achieved >75% clearance 2 treatments—40% >75% clearance 3 treatments—40% >75% clearance	PIH 2/29 (7%)—resolved in 6 months	Picosure	No
Sakio et al. [20]	Nevus of Ota	15	Retro review	750 ps 2.2–2.5 spot size 4.07–6.37 J/cm^2	755 nm	Effective clearance of lesions after 2–3 treatments at 4-month intervals	Post-inflammatory erythema and hyperpigmentation lasting 1.4 and 2.7 months, respectively	Picosure	No
Levi et al. [21]	Verr epider nevus	6	Case series	III	532 nm 375 ps 3 mm spot 1.8 J, 3 passes 2–6 treatments, 8–10-week intervals	3.7/4 clearance 12 months post-final treatment	Severe blistering: authors hypothesize that it was a key to inducing good clinical outcome	Picoway	No
Alegre-Sanchez et al. [22]	Flat and raised epidermal lesions	37	Retro review	I–IV	755 nm 550–750 ps 2.5–3.5 mm spot 2–4 J	61% clearance of flat lesions 65% clearance of raised lesions Mean treatments = 3	One case of bullae formation	Picosure	No
Yang et al. [23]	Freckles in Chinese	20	PRLC	III–IV	Facial halves randomized to be treated with either: 755 nm 750 ps spot size not provided 4.4 J/cm^2 Or 755 nm	PSAL vs. QSAL 76.9% vs. 75.6% clearance rate No significant difference in efficacy or downtime	No unexpected side effects	Picosure vs. Accolade	No

(*Continued*)

TABLE 1. (*Continued*)

Author/date	Lesion	*N*	Study type	Skin type	Settings	Results	Complications	Device	Fractionated
Vachiramon et al. [24]	Lenti-gines in Asians	30	PRLC	III–IV	70 ns Spot size not provided 6.92 J/cm^2 1 treatment 2-month follow-up 2 lentigines per subject were randomized to either PS 532 or QS 532: PS 532 3 mm spot 375 ps 0.3–0.9 J/cm^2 Treat to whitening QS 532 5 ns 3 mm spot 1.4–1.7 J/cm^2 Treat to whitening 1 treatment 12-week follow-up	Investigator evaluation detected no significant difference in efficacy Subjects rated 60.7% of PS-treated lesions as having excellent clearance vs. 32.1% with QS, but not statistically significant; subjects were significantly more satisfied with PS lesions	No differences in healing time nor adverse events 7.1% PIH with both	Picoway vs. revlite	No
Wong et al. [25]	Hori	3	Case series	III–V	1064/532 nm with fractional microlens array 750 ps 3–5 mm spot 1.8–3.0 J/cm^2 at 1064 nm 0.1–0.3 J/cm^2 at 532 nm 6–9 treatments at 4–12-week intervals over 9–12 months with a 2-month follow-up evaluation	Good to excellent clearance of lesions	None	Enlighten	Yes

(*Continued*)

TABLE 1. (*Continued*)

Author/date	Lesion	*N*	Study type	Skin type	Settings	Results	Complications	Device	Fractionated
Negishi et al. [26]	Lentigines in Asian	20	Prospective OLT	III–IV	532 nm 750 ps 0.2–0.5 J, 3–4 mm spot Endpoint of slight whitening 93% of lesions received 1 treatment, 7% received 2 Compared ns vs. ps effect histologically and with EM on one patient with arm lentigines—ns settings were 532 nm, 5–10 ns, 3 mm spot, 1.2 J; ps settings were 532 nm, 750 ps, 4 mm spot, 0.5 J	Greater disruption of DEJ on H + E with ns settings; equivalent melanosome destruction on EM but greater non-specific organelle destruction with ns 77% of lesions achieved 76–100% improvement at 3-month follow-up	4.65% PIH rate	Enlighten	No
Chan et al. [27]	Lentigines in Asian	20	Prospective OLT	III–IV	532 nm 750 ps 0.2–0.5 J,	At 12 weeks: 90% of patients had moderate to significant improvement as rated by the investigator; 75% of patients rated themselves as having moderate to significant improvement There was no worsening of any	10.2% PIH rate that all resolved by 12 weeks; mean time to resolution of 6.5 weeks 1 lesion hypopigmented but	Enlighten	No

(*Continued*)

TABLE 1. (*Continued*)

Author/date	Lesion	*N*	Study type	Skin type	Settings	Results	Complications	Device	Fractionated
					4 mm spot Up to 3 treatments at 4–6-week intervals depending on clinical response 12-week follow-up	lesion at either 4 or 12 weeks post-final treatment	resolved by 12 weeks 1 case of persistent erythema at 3 weeks, resolved by 7 weeks		
Ge et al. [28]	Nevus of Ota	56	Randomized, split-lesion comparison	III–IV	755 nm 750 ps	PASL achieved significantly better clinical results in significantly fewer treatment sessions	Almost all parameters shown to be significantly better with PS laser vs. QS laser, but the absolute clinical differences seemed relatively small	Picosure vs. Accolade	No
					2–4 mm spot	PSAL had 53% complete clearance rate vs. 21% with QSAL			
					1.59–6.37 J/cm^2	Patients were significantly more satisfied with PSAL vs. QSAL			
					5 Hz	PSAL had 45% of patients "very satisfied" vs. 19% for QSAL			
					755 nm	PSAL significantly less painful than QSAL on VAS			
					70 ns	PSAL significantly shorter duration of post-treatment scabbing than QSAL			
					3 mm spot	PSAL significantly less PIPA than QSAL			
					5–7 J/cm^2 5 Hz Up to 6 treatments at 12-week intervals 3-month follow-up	Bleeding and blistering equivalent between the two groups			

(*Continued*)

TABLE 1. (*Continued*)

Author/date	Lesion	*N*	Study type	Skin type	Settings	Results	Complications	Device	Fractionated
Kung et al. [29]	Benign pigments	12	OLT	III–IV	1064/532 nm	Good to excellent response for freckles and lentigines in 1–3 treatments	Purpura 12.9%	Picoway	No
					450/375 ps		Edema 40.3%		
					Lentigines: 532 nm, 3 mm spot, 0.49–0.64 J/cm^2	Good to excellent response in CALM after 3–5 treatments	Erythema 80.6%		
					CALM: 532 nm, 3–6 mm spot, 0.36–0.87 J/cm^2	25%, 50%, and 25% fair, good, and excellent response, respectively for melasma with 8–9 treatments	Crusting 1.6%		
					Freckles: 532 nm, 3 mm spot, 0.36–0.67 J/cm^2		Pinpoint bleeding 6.5%		
					Melasma: 1064 nm, 6 mm spot, 0.54–1.22 J/cm^2		Hyperpigmentation 4.8%		
					Hori's macules: 1064 nm, 3–4 mm spot, 1.86–3.67 J/cm^2; 532 nm, 3 mm spot, 0.49 J/cm^2		Blistering 6.5%		
					3-month follow-up		All mild to moderate, transient		

TABLE 2. Other Non-Melasma Pigmented Conditions

Author/date	Lesion	*N*	Study type	Skin type	Settings	Results	Complications	Device	Fractionated
Rodrigues et al. [30]	Mino	3	Case series	II	755 nm 750 ps 3 mm spot 2.8 J 1–2 treatments	Split face comparison with QS Nd:YAG showed picosure superior	None	Picosure	No
DiGiorgio et al. [31]	Argyria	1	Case report	II	755 nm 750 ps 4 mm spot 1.59 J 1 treatment	80% resolution	Significant edema resolved with 5 days	Picosure	No
Moore et al. [32]	Mino pig post-sclero	1	Case report	III	755 nm 750 ps 6 mm spot 0.71 J 2 treatments	Lesions treated previously with QS alex, yag, ruby with no change; picosure led to complete resolution	None	Picosure	No
Sasaki et al. [33]	Mino	1	Case report	IV	755 nm 750 ps 2 mm spot 6.37 J 1 treatment	Near complete resolution 1 year post-treatment	None	Picosure	No
Friedman et al. [34]	Argyria	1	Case report	I	755 nm 750 ps 3 mm spot 2.83 J 2 treatments	90% resolution	None	Picosure	No
Vanaman Wilson et al. [35]	Infraorbital dark circles	1	Case report	IV	755 nm 550 ps 6 mm spot 0.57 J FLA 1 treatment	90% resolution in 3 months	None	Picosure	Yes
Vanaman Wilson et al. [36]	Infraorbital hyper	29	Prospective open label	I–IV	755 nm 750 ps 6 mm spot 0.71 J 3 treatments spaced 3 weeks apart 1064/532 nm 450/375 ps	Significant improvement after 3 treatments with 755, no improvement with 1 treatment Yag	None	Picosure Picoway	Yes

(*Continued*)

TABLE 2. (*Continued*)

Author/date	Lesion	*N*	Study type	Skin type	Settings	Results	Complications	Device	Fractionated
					6 mm spot 0.16–1.3 J Two passes, one treatment				
Wu et al. [37]	Stasis	1	Case report	II	755 nm 750 ps 3.3 mm spot 2.34 J 3 treatments 1–2-month intervals	90% clearance 1 month post-final treatment	None	Picosure	No
Barrett et al. [38]	Mino	1	Case report	II	755 nm 750 ps 6 mm spot 0.71 J 4 treatments, 1-month interval	Near complete resolution; previous 5 treatments with 1,064 and 532 QS yag ineffective	None	Picosure	No
Mendez et al. [39]	Exogenous ochronosis	1	Case report	IV	1064/532 nm holographic beam splitter 6 mm spot 1064 nm: 1.3–2.9 J/microbeam 450 ps 532 nm: 0.18–0.3 J/microbeam 375 ps 9 treatments at 2-week intervals	Marked improvement	None	Picoway	Yes
De Souza et al. [40]	Phakomatosis cesioflammea	1	Case report	IV	Combination of QS ruby, Nd:YAG, and PS Nd:YAG	15 treatments with QS laser then 3 treatments with PS laser—continued improvement with PS laser after plateau with QS laser	None	Picoway	No
Shao et al. [41]	Argyria	1	Case report	II	755 nm 6 mm spot	Previous failure with QS Nd:YAG; significant clinical clearance with PS laser after 1 treatment Clearance of silver deposits on pre- and	None	Picosure	No

(*Continued*)

TABLE 2. (*Continued*)

Author/date	Lesion	*N*	Study type	Skin type	Settings	Results	Complications	Device	Fractionated
						post-treatment biopsies visualized under light microscopy			
					0.71 J/cm^2 Single full face treatment —pulses not specified	Scanning electron microscopy: silver particle sizes decreased from 25 to 100+ nm to 4–15 nm; morphological change from intact spherules to shattered "star-burst"			
Weiss et al. [42]	Argyria	1	Case report	II	755 nm	Instant clearance of argyria discoloration observed with both lasers	None	Picosure vs. QX	No
					4.5–5.5 mm spot 0.84–1.26 J/cm^2 750 ps 1064 nm	No clinically apparent difference in efficacy between two lasers			
					5 mm spot 2.5 J/cm^2 5 ns				
Tsai et al. [43]	Drug melanonychia	1	Case report	IV	1064 nm 3–4 mm spot 4.8–5.0 J/cm^2 750 ps 1 treatment 3-month follow-up	Complete resolution of nail pigmentation	None	Unknown	No
Kok et al. [44]	Imatinib hyperpigmentation	1	Case report	IV	755 nm 550 ps 3 mm spot size 2.33 J/cm^2 5 treatment sessions at 2-month intervals 6-month evaluation	>75% reduction of hyperpigmentation	None	Picosure	No
Wu et al. [45]	Lichen planus pigmentosus	1	Case report	IV	Combination treatment with 0.1% tacrolimus ointment BID, hydroxychoroquine 200 mg BID, and 1064 nm picosecond Nd:YAG laser 3 laser treatment sessions at 4-month intervals	Significant improvement of hyperpigmentation	None	Unknown	Yes

TABLE 3. Rejuvenation

Author/date	Lesion	*N*	Study type	Skin type	Settings	Results	Complications	Device	Fractionated
Wu et al. [46]	Chest photodamage	20	Prosp OLT	I–IV	755 nm 6 × 6 mm spot 0.71 J 750 ps 2–4 passes 6,631 ± 1,915 pulses per treatment 2–4 treatments, 3 weeks apart	Significant improvement in dyspigmentation, texture, and keratoses Minimal improvement in rhytides No improvement in erythema	1 case of urticarial reaction Pain 3.7/10	Picosure	Yes
Ge et al. [47]	Facial photoaging	10	PRLC	III–IV (5 skin type III, 5 skin type IV)	755 nm Skin type III: 6 mm spot 0.71 J/cm^2 Skin type IV: 8 mm spot 0.40 J/cm^2 1,500 pulses per treatment 4 treatment sessions at 2-week intervals to right face; left served as untreated control; evaluation at 2-month follow-up 2 blinded evaluators	Global Photoaging Scale (GPS): Significant improvement on treated side Asian Photographic Scale (APS): Significant improvement in wrinkling, trend toward improvement in pigmentation 60% of subjects had improvement in nasolabial fold	Treatment pain: 6.0–6.9/10 24 hours of transient erythema and edema	Picosure	Yes
Khetarpal et al. [48]	Photodamage	20	Prosp OLT	I–III	755 nm with DLA 750 ps 6 mm spot size 0.71 J/cm^2 6,253 pulses per treatment 4 treatments at 2–3-week intervals 3-month follow-up after final treatment	Subject satisfaction: 93% Three blinded evaluators correctly identified treatment photo 69% of time	Swelling, pain, redness, crusting was mild and resolved within 48 hours Pain level 4.2/10	Picosure	Yes
Saluja [49]	Chest and	20	Prosp OLT	II–IV	10—chest	Significant improvement	None	Picosure	Yes

(*Continued*)

TABLE 3. (*Continued*)

Author/date	Lesion	*N*	Study type	Skin type	Settings	Results	Complications	Device	Fractionated
	hands				10—bilateral dorsal hands 755 nm 6 × 6 mm spot 0.71 J 4 treatments 3-week intervals 1- and 3-month follow-up	and satisfaction observed			
Weiss et al. [50]	Facial wrinkles	40	Prosp OLT	I–IV	755 nm 6 × 6 mm spot 0.71 J 750 ps 5,000 pulses per treatment 4 treatments, 1-month interval	FWS improvement from 5.48 to 3.47 ($P < 0.05$) Mild to moderate improvement in fine lines Mod to marked improvement in dyspigmentation Minimal improvement in erythema Histology—significant increase in collagen and elastic fibers	1 patient reported erythema ×2 days 1 patient reported edema ×4 days	Picosure	Yes
Berstein et al. [51]	Facial photoaging	27	Prosp OLT	I–IV	14 subjects—1064 nm 1.3–2.5 mJ/beam 5 treatments, 1-month interval 10 subjects—532 nm 1–1.4 mJ/beam 4 treatments, 1-month interval	>20% improvement in 57% of subjects No significant difference between 1,064 vs. 532	1 patient had post-treatment erythema ×7 days	Picoway	Yes
Serra et al. [52]	Photodamage	20	Randomized comparison trial	I–IV	Fractional 1927 nm thulium fiber vs. 755 nm picosecond alexandrite 1927: 2 treatments at 6-week intervals 10 mJ 40% coverage 4–6 passes 755: 4 treatments at the 3-week interval with both	Global photoaging scale, GAIS, and FWS all improved significantly more with PS laser vs. 1927 Pigmentation and erythema significantly better with PS laser vs. 1927 No difference in radiance, smoothness, and pore size Significantly greater subject satisfaction with PS laser vs. 1927 Significantly greater subject rated the improvement in	Significantly less erythema with PS laser at 4 weeks, but equal at 12 weeks Significantly more pain with 1927	Picosure vs. fraxel dual	Yes

(*Continued*)

TABLE 3. (*Continued*)

Author/date	Lesion	*N*	Study type	Skin type	Settings	Results	Complications	Device	Fractionated
					fractionated and non-fractionated modes Non-fractionated mode used at 3–4 mm spot to treat discrete lesions to frosting Diffractive lens array 6 mm spot 0.71 J/cm^2 750 ps 5,000–8,000 pulses 12-week follow-up	photodamage and wrinkling with PS laser vs. 1927			
Wat et al. [53]	Rejuvenation in Chinese	18	OLT	III–IV	755 nm with diffractive lens array 750 ps 6 mm spot 0.71 J/cm^2 10 Hz 4 passes 6 treatments at 4-week intervals 3-month follow-up	Significant improvement in skin texture and dyspigmentation detected at 1 month and persistent to 3 months No reduction in pore size nor skin laxity Rhytids seemed to improve at 1 month but was not sustained at 3 months	No PIH	Picosure	Yes
Gold [54]	Wrinkles	20	Prosp OLT	II–IV	1064/532 nm holographic beam splitter 1064 nm: 2.3 mJ/microbeam, 6 mm spot, 1,373 ± 208 pulses, 2 passes 532 nm: 0.58 mJ/microbeam, 6 mm spot, 1,246 ± 132 pulses, 2 passes 4 treatments at 1-month intervals 12-week follow-up evaluation	2.1 point improvement in FWS assessment of the perioral and periorbital regions ($P < 0.05$) 75% of subjects were either “very satisfied” or “satisfied”	Pain level 3.7/10 No unexpected adverse events	Picoway	Yes

(*Continued*)

TABLE 3. (*Continued*)

Author/date	Lesion	*N*	Study type	Skin type	Settings	Results	Complications	Device	Fractionated
Yim et al. [55]	Photodamage	25	PRLC	III–IV	Picosecond 1064 nm Nd:YAG vs. micro pulse 1064 nm Nd:YAG	Investigator 5-point scale improvement assessment: Significantly more improvement in visible pores at lateral canthal area in pico half (54.2% vs. 41.7%, $P < 0.05$)	Pain was significantly greater on pico side (3.65 ± 1.70 vs. 1.28 ± 1.28 out of 10, $P < 0.05$)	Picocare vs. Excel V	Yes
					PSYAG:	Wrinkle improvement was 12.5% vs. 4.2% pico vs. micro, but not significant ($P = 0.125$)	No serious adverse events reported		
					Microlens array	3D digital skin analysis: both pore size and wrinkles in the lateral canthal areas showed greater improvement with pico treatment vs. micro (16.4% vs. 0.5% $P = 0.01$ and 41.3% vs. 3.9% $P = 0.048$, respectively)			
					8 mm spot 0.6–0.8 J/cm^2 450 ps 1,500 total pulses Micropulse YAG: 8 mm spot 4 J/cm^2 0.3 ms 1,500 total pulses 5 treatments at 2-week intervals 12-week follow-up evaluation after final treatment session	Subject satisfaction was equal on both sides			

TABLE 4. Melasma

Author/date	Lesion	*N*	Study type	Skin type	Settings	Results	Complications	Device	Fractionated
Lee et al. [56]	Melasma	3	Case series	IV	755 nm 550 ps 6 mm spot 0.57 J 6–14 sessions spaced 2 weeks apart	Fair to good improvement	No post-treatment erythema noted	Picosure	No
Choi et al. [57]	Melasma	39	PRLC	III–V	Split face with 2% HQ as control	Colorimeter: significantly more lightening on the laser side 1 week, 1 month, 2 months, and 3 months after treatment	No incidence of rebound or PIH	Pico+4	No
					1064 nm: 7–10 mm spot 0.2–1.5 J 2–4 passes 595 nm: 5 mm spot 1–2 passes 0.1–0.55 J 750 ps 5 treatments, 1-week interval 1-, 2-, 3-month follow-up	MASI: significant improvement on laser-treated side only at 1 week	Dermatitis 5%		
Chalermchai et al. [58]	Melasma	30	PRLC (prosp, split face, rando, eval blind)	III–IV	Full face—4% HQ; random half-face—fractionated 1064 nm 6 × 6 mm 1.3–1.5 mJ/beam 450 ps 8–12% coverage 400–1,000 pulses 4 Hz Endpoint mild erythema	4-week follow-up: Significant improvement in MASI with laser treatment vs. HQ control side (absolute difference 3.52 vs 4.18)	Mild erythema (6.7%), mild desquamation 6.7%), mild burning sensation (3.3%)	Picoway	Yes

(*Continued*)

TABLE 4. (*Continued*)

Author/date	Lesion	*N*	Study type	Skin type	Settings	Results	Complications	Device	Fractionated
					Follow-up evaluation 4 weeks after final laser treatment				
Lee et al. [59]	Melasma	12	PRLC	III–IV	PSAL vs. QS YAG PSAL: 4.4–5.1 mm spot, 0.88–1.18 J/cm^2, 650 ps, 3 passes, 1,000 pulses QS YAG: 5 ns Pass 1: 8 mm spot, 2 J/cm^2 Pass 2: 6 mm spot, 3.5 J/cm^2 Pass 3: 4 mm spot, 3.2 J/cm^2 Endpoint: mild erythema with edema but no petechiae 4 treatments at 1-month intervals 3-month follow-up after final treatment	Pigment clearance was faster and significantly better on the PSAL side in both physician and patient assessments	No unexpected adverse events No report of rebound pigmentation	Picosure vs. Medlite	No
Wang et al. [60]	Melasma	26	Randomized single-blind comparison		Group A1: 755 nm diffractive lens array	Significant improvement noted in MASI score in all three groups at the final evaluation time point; no significant differences between groups	Everyone applied SPF50 + Q2H for the duration of the study—no control group to exclude the possibility that improvements were not due to increased sun protection alone	Picosure	Yes
				8 mm spot	VISA analysis	Baseline MASI			

(*Continued*)

TABLE 4. (*Continued*)

Author/date	Lesion	*N*	Study type	Skin type	Settings	Results	Complications	Device	Fractionated
					suggested improvement in spots, pores, wrinkles in both laser groups	scores were 3–4 points lower in group A1 vs. A2 and B—claimed to be non-significant difference but used parametric testing with ANOVA, which is questionable at such small sample sizes			
				0.4 J/cm^2		A2 had a follow-up evaluation at 1 month but not 3 months—not comparable			
				750 ps		VISIA analysis only done on laser groups—why not analyze TCC group as well?			
				2 passes, 2,500 pulses, endpoint mild erythema 3 treatment sessions at 4-week intervals Group A2: 755 nm diffractive lens array 8 mm spot 0.4 J/cm^2 750 ps 2 passes, 2,500 pulses, endpoint mild erythema 5 treatment sessions at 4-week intervals		18.2% PIH rate in A2; 33.3% irritation in B			

(*Continued*)

TABLE 4. (*Continued*)

Author/date	Lesion	*N*	Study type	Skin type	Settings	Results	Complications	Device	Fractionated
				Group B: TCC consisting of fluocinolone acetonide 0.01%, hydroquinone 4%, and tretinoin 0.05% applied QHS for 8 weeks, then twice weekly for 6 weeks, then once weekly for 6 weeks All subjects evaluated at 1 month following the final treatment for group A2					
Chen et al. [61]	Melasma	20	OLT	IV	755 nm 8 mm spot 0.4 J/cm^2 10 Hz 2 passes, 2,000–2,500 pulses 3 treatments at 4–6-week intervals 4-week follow-up	MASI: Significant improvement from baseline (9.0 ± 4.8 vs. 6.5 ± 3.7) VISIA: Significant improvement in spots and porphyrins	5% PIH	Picosure	Yes
Lyons et al. [62]	Melasma	10	PRLC vs. 6% HQ	II–IV	9 weekly treatments to randomized facial	More improvement on the treated side	None	PiQo4	No

(*Continued*)

TABLE 4. (*Continued*)

Author/date	Lesion	*N*	Study type	Skin type	Settings	Results	Complications	Device	Fractionated
					half with variable treatment settings and variable combinations of 1064/532 nm; pulse duration 800 ps Follow-up evaluations performed at 1 week post-final treatment	vs. untreated side per investigator and subject assessment			

(Korean, Vietnamese, Chinese, and Hispanic ethnicities) and reported 78% of lesions had between 75 and 100% clearance after a single treatment session. Treatment settings ranged from a 4–6 mm spot size and 0.5–0.8 J/cm^2. Interestingly, only 1% had worsening due to PIH [15]. In a later study, Negishi et al. used a 750 picoseconds pulsed 532 nm frequency double Nd:YAG laser in a prospective open-label trial involving lentigines in 20 Asian patients. The laser settings were 3–4 mm spot size and 0.2–0.5 J/cm^2. Ninty-three percent of lesions received one treatment session and 77% of patients achieved 76–100% improvement at a 3-month follow-up time point. The rate of PIH was reported as 4.65%. A further histological analysis was conducted comparing the effects of this picosecond laser versus a nanosecond laser with a 5–10 nanoseconds pulse duration, 532 nm wavelength, 3 mm spot size, and 1.2 J/cm^2. This analysis revealed a greater amount of dermal–epidermal junction (DEJ) disruption with the nanosecond laser. Additionally, electron microscopy demonstrated a similar degree of melanosome destruction but a greater degree of non-specific cellular organelle damage with the nanosecond laser [26]. A later study by Chan et al. confirmed these data, but with a reported PIH rate of 10.2% [27]. The PIH rate between 5 and 10% as reported in the latter two studies is consistent with the authors' clinical experience, whereas the low rate of 1% seen by Guss et al. may have been an underestimation due to the retrospective nature of their study, differences in methodology used to calculate PIH rate, and low sample size.

CALM has been studied in one retrospective review involving 16 patients [17]. Artzi et al. used a 375 picoseconds pulsed 532 nm frequency double Nd:YAG laser at 4–5 mm spot size and 0.8–1.6 J/cm^2. One to four treatment sessions were administered and the investigators reported that 15/16 patients achieved significant to complete resolution of their lesions with one non-responder [17]. CALMs with jagged, ill-defined borders of the coast of Maine subtype may respond better to laser treatment [92].

For Nevus of Ota, there have been two case series; two retrospective reviews; and one randomized split-lesion double-blind comparison trial study involving a cumulative total of 103 subjects [13,16,19,20,28]. In one retrospective review of 29 Chinese patients, a 750 picoseconds pulsed 755 nm picosecond alexandrite laser achieved >75% clearance in 40% of patients after two treatment sessions. These results were achieved utilizing a 2–4 mm spot and 1.96–6.37 J/cm^2. The rate of PIH was reported as 7% [19]. In the case of Hori's macules, the picosecond alexandrite laser demonstrated clear superiority as compared with the nanosecond alexandrite laser in a 33 patient split-face randomized, controlled trial conducted by Yu et al. The picosecond alexandrite laser settings were 2–2.5 mm spot size, 750 picoseconds pulse duration, and 4.07–6.37 J/cm^2 whereas the nanosecond device was utilized at a 3 mm spot size, 70 nanoseconds pulse duration, and 6–8 J/cm^2. Three treatments were delivered over a 6-month interval. The picosecond laser demonstrated a

TABLE 5. Scar Revision

Author/date	Lesion	*N*	Study type	Skin type	Settings	Results	Complications	Device	Fractionated
Brauer et al. [9]	Acne scar	20	Prosp OLT	I–V	755 nm 6 × 6 mm 0.71 J 750 ps 5 Hz 6 treatments, 4–8 week intervals Mean 3,072 pulses per treatment	24–27% scar volume reduction Also noted significant improvement in skin texture and pigmentation secondarily Increased collagen III and elastic fibers	Maximum 2 days erythema	Picosure	Yes
Bernstein et al. [8]	Acne scar	31	Prosp OLT	II–V	21 subjects treated with 1064 nm: 1.3–2.8 J 6 × 6 mm spot 4 treatments, monthly intervals 450 ps 10 subjects treated with 532 nm: 1.1–1.5 mJ/microbeam 4 treatments, monthly intervals 375 ps	81% showed some improvement, 48% showed >20% improvement, 26% showed >30% improvement	Maximum erythema duration = 4 days; majority resolved with 1–2 days No post-inflammatory pigmentary alteration noted	Picoway	Yes
Zhang et al. [63]	Acne scar	20	Prosp OLT	III–IV (chinese)	755 nm 6 mm spot 0.71 J/cm^2 750 ps 5 Hz 5 passes 3 treatments at 4–6-week intervals	ECCA: Decreased from 197.75 ± 35.26 to 142.00 ± 35.92 (28% improvement, $P = 0.000$) 70% of patients showed >50% improvement of PIE Patient reported improvement: 2.3 ± 1 out of 3 50% of patients were "satisfied"; 30% "very satisfied"	3.2/10 pain A few days of mild and transient erythema, edema, and scabbing	Picosure	Yes

(*Continued*)

TABLE 5. (*Continued*)

Author/date	Lesion	*N*	Study type	Skin type	Settings	Results	Complications	Device	Fractionated
					Follow-up evaluation: 2 months after final treatment				
Zaleski Larsen et al. [64]	Striae alba	20	PRLC	II–IV	523/1064 nm with holographic lens	Significant improvement in texture and atrophy, but no difference between treatment halves	None	Picoway	Yes
					450 ps	Striae density was not significantly improved		vs.	
					6 mm spot size	Pain significantly decreased on picosecond side		Resurfx	
					1.3 mJ/microbeam at 1064 nm 0.4 mJ/microbeam at 532 nm 4 passes per wavelength	Significantly faster healing time associated with picosecond side			
					1565 nm 12 mm square spot Density: 400 dots/cm^2 Energy: 40 J 1 pass				
					3 treatments delivered at 3-week intervals 6-month follow-up				
Chayavichitsilp et al. [65]	Acne scar	30	PRLC	III–IV	1064 nm with fractional lens array	ECCA: Both treated halves had significant improvement; ps side –38.89% vs. Er:fiber side –33.33%; no significant difference	Erythema and hyperpigmentation were the same on both sides	Discovery PICO vs. FineScan	Yes
					8 mm	Patient rated that improvement and satisfaction was the same on both sides	Immediate pinpoint bleeding was significantly greater on ps side		
					0.3–0.4 J/cm^2 10 Hz 1 pass	Significantly greater pore count reduction with Er:fiber (15.4% vs. 7.5%, $P < 0.05$)	Pain was significantly greater on Er:fiber side		
					1550 nm Er fiber 100–400 spots/cm^2 25–30 J/cm^2 2 passes 4 treatments at 4-week				

(*Continued*)

TABLE 5. (*Continued*)

Author/date	Lesion	*N*	Study type	Skin type	Settings	Results	Complications	Device	Fractionated
					intervals Follow-up at 4 and 8 weeks				
Dai et al. [66]	Acne scar	20	Prosp OLT	III–V	1064 nm with fractional lens array	Blinded evaluator: mean 3/10 improvement; 85% showed some improvement; 45% showed improvement of at least 3/10	Pain 6/10	Discovery PICO	Yes
					450 ps	Subjects evaluation: median 8/10 improvement but only 55% "satisfied" and 45% "very satisfied"	Median healing time: 4 days, range 1–10 days		
					8 mm 0.3–0.4 J/cm^2 10 Hz 2 passes for an estimated 10% density, 1,200–1,600 pulses 3 treatments at 4-week intervals 3-month follow-up	FASQoL: Significant improvement in quality of life pre vs. post-treatment	No pigmentary alteration at 1 week, 1 month, or 3 months		
Koren et al. [67]	Hyperpigmented scars	16	Case series	II–VI	1064 nm with holographic lens	Causes of hyperpigmented scars: Burn injury [4], road accident [8], leishmaniasis [1], surgical operation [2], and unspecified disease [1]	None	Picoway	Yes
					6 mm spot 1.7–2.5 J/cm^2 3–8 treatment sessions at 3–6-month intervals Follow-up 6 months after final treatment	GAS improvement 3.31 ± 0.57 out of 4 Patient satisfaction 2.6 ± 0.5 out of 3 Melanin index $39.11 \pm 11.58\%$ improvement			
Choi et al. [68]	Hypertrophic scar	24	Retro review	III–V	1064 nm 750 ps 7.94 mm spot	70.83% of scars were younger than 6 months VSS improved significantly from	No unexpected side effects	PICO + 4	No

(*Continued*)

TABLE 5. (*Continued*)

Author/date	Lesion	*N*	Study type	Skin type	Settings	Results	Complications	Device	Fractionated
					0.93 J/cm^2 1–7 treatments at 3–13 week intervals	5.33 ± 1.37 to 2.71 ± 1.27			
Guida et al. [69]	Atrophic surgical scars	9	Retro review	II–III	1064 nm with fractional lens array, which splits the beam into 60 microbeams of 200 μm diameter	66% of scars improved in blinded evaluation	None	Discovery PICO	Yes
					450 ps	50% of subjects were "very satisfied", 40% "satisfied", 10% "not satisfied"			
					8 mm spot size 10 mJ/microbeam 15% density delivered over 3 passes 3 treatments at monthly intervals 6-month follow-up evaluation	Reflectance confocal microscopy revealed rearrangement of collagen fibers into a "net-like" configuration			
Guida et al. [70]	Atrophic and hypertrophic surgical scars	16	Retro review	II–III	1064 nm with fractional lens array, which splits the beam into 60 microbeams of 200 μm diameter	VSS—improvement of 2.4 ± 0.7, $P < 0.05$	None	Discovery PICO	Yes
					450 ps	95% of scars improved by both investigator- and subject-reported outcomes			
					8 mm spot size	44% of subjects "very satisfied", 50% "satisfied", 6% "not satisfied"			
					10 mJ/microbeam	3D imaging revealed 5.1 ± 2.4 point improvement in texture, $P < 0.05$			
					15% density delivered over 3 passes	Reflectance confocal microscopy revealed a significant reduction in epidermal thickness for hypertrophic scars but not atrophic scars			
					3 treatments at monthly intervals	Also visualized "net-like" reconfiguration of			

(*Continued*)

TABLE 5. (*Continued*)

Author/date	Lesion	*N*	Study type	Skin type	Settings	Results	Complications	Device	Fractionated
					6-month follow-up evaluation	collagen fibers			
Huang et al. [71]	Acne scar	53	Retro review	III–IV	755 nm with DLA 750 ps 6 mm spot size 0.71 J/cm^2 2,500 pulses delivered over 3–6 passes Mean number of treatments: 4.28 (range 2–12) Mean follow-up time: 7.3 weeks (range 2–26 weeks) Treatment interval: 2–6 weeks	Efficacy rated by photographic evaluation and stratified by treatment number: 2 treatments—35% 3 treatments—36% 4 treatments—43% 5 treatments—33% 6 treatments—58% >6 treatments—42%	2 cases of transient and self-resolving PIH	Picosure	Yes
Yang et al. [72]	Acne scar	20	OLT	III–IV	All treatments done with holographic fractionated lens 1st pass: 532 nm, 0.3–0.5 J/cm^2, 5 Hz, full face 2nd pass: 1064 nm, 1.5–1.9 J/cm^2, 8 Hz, full face 3rd pass: 1064 nm, 2.1–2.5 J/cm^2, 8 Hz on deeper scars Total pulses: 2,500–3,000 6 treatment sessions at 1- month interval Final evaluation 3 months post-final treatment session	Improvement of GSS quantity and quality scores respectively from baseline: 15.22 and 3.00 to 10.61 and 2.33 ($P < 0.05$) Improvement of VAS: 4.28–2.00 ($P < 0.05$)	Pain: 3.28/10 Some purpuric spots lasting 2–3 days No PIH No scarring	Picoway	Yes

TABLE 6. Tattoos

Author/date	Lesion	*N*	Study type	Skin type	Settings	Results	Complications	Device	Fractionated
Ross et al. [73]	Black	16	PRLC, split tattoo	N/A	1064 nm, 35 ps, 1.4 mm, 0.65 J, 10 Hz vs. 10 ns	Maintaining all other parameters the same, picosecond pulse far more effective than nanosecond pulse	None	N/A	N
Herd et al. [74]	Ps vs. ns pig model	6	Pig model	N/A	795 nm 500 ps vs. 752 nm 50 ns Fluence and spot size kept identical: 6.11, 4.24, 2.39 J and 1.25, 1.5, and 2 mm, respectively	Picosecond laser significantly has better clearance	None	Experimental	N
Izikson et al. [75]	Black in pig model	1	Animal model	N/A	758 nm 500 ps laser used at three settings 1.3 mm spot, 13–16 J; 1.9 mm spot, 6–7.5 J; 2.9 mm spot, 2.5–3.9 J vs. 755 nm 30–50 ns used at typical clinical settings (3 mm spot, 8 J)	Picosecond-pulsed laser superior for black ink clearance at ALL settings	None	Prototype device	N
Brauer et al. [76]	Blue and green	12	Case series	II–IV	755 nm 750 ps 3–3.6 mm spot 2–2.83 J	1–2 treatments resulted in >75% clearance of blue and green	None	Picosure	N
Saedi et al. [77]	Blue or black	12	Prosp OLT	I–V	755 nm 2.5–3.5 mm spot 500–900 ps 2.1–4.1 J Up to 10 treatments spaced 4–8 weeks	After 2–4 treatments, 75% achieved >75% clearance	20% hypopigmentation at 3 months, 13% hyperpigmentation	Picosure	N
Au et al. [78]	Tattoo bullae	95	Retro review	N/A	755 nm 2.94–3.31 mm spot 2.67–3.37 J Fractionated CO_2—10–60 mJ, 5–40% density	Significant decrease in bullae formation when treated with Fx CO_2—32% vs. 0%	None	Picosure	N
Alabdulrazzaq, et al. [79]	Yellow	6	Case series	II–III	532 nm 2.5–3.3 mm spot 1.1–1.4 J 450–500 ps Up to 10 treatments at 6–8 week intervals	1–4 treatments, all achieved >75% clearance	None; pain with injection lido 1.3/10, pain without 6/10	Cynosure study prototype	N

(*Continued*)

TABLE 6. (*Continued*)

Author/date	Lesion	*N*	Study type	Skin type	Settings	Results	Complications	Device	Fractionated
Bernstein et al. [80]	All colors—black, green, red, purple, yellow, blue	31	Prosp OLT	I–IV	1064/532 450/350 ps 3–5 mm spot 1.4–5.3 J for 1064 0.4–2.1 J for 532 Up to 7 treatments	After 7 treatments: 92% clearance of black 85% clearance of yellow 80% clearance of red 78% clearance of purple 65% clearance of green 43% clearance of blue	Injection lido used 13% mild hyperpigmentation 6% mild hypopigmentation at 3 months	Picoway	N
Bae [81]	Paradoxical darkening	2	Case series	II	1064 nm 2.7–4.5 mm spot 0.4-1.4 J	Improvement of paradoxical darkening of red tattoos	Injection lido used	Cynosure study prototype	N
Freidman et al. [82]	Black and red	1	Case study	VI	Three treatments: Treatment 1—1064 nm, 10 mm spot, 0.5 J and 532 nm, 10 mm spot, 0.25 J Treatment 2—1064 nm, 9 mm spot, 0.6 J and 532 nm, 9 mm spot, 0.3 J Treatment 3—1064 nm, 6 mm spot, 1.4 J and 532 nm, 9 mm spot, 0.3 J	After 1.5 months of treatment, 75% clearance of black ink, 90% clearance of red ink	None	Picoway	N
Lee et al. [83]	Black and red	6	Case series	IV (Korean)	755 nm 2–3 mm spot 2.68–5.25 J 550–750 ps	1–5 treatments to achieve >75% clearance	50% hypopigmentation at 3 months	Picosure	N
Pinto et al. [84]	Ps vs. ns, black	30	Single-blind split tattoo RCT	N/A	450 ps vs. 5 ns Exact settings not disclosed—authors state that settings were used "as high and defensible" as possible with an endpoint of epidermal whitening with minimal pinpoint bleeding Specs of each device show that for equal spot size, the ns device potentially generates	No significant difference in clearance after 2 treatments	Pain significantly reduced on picosecond-treated side	Picoway vs. Medlite C6	N

(*Continued*)

TABLE 6. (*Continued*)

Author/date	Lesion	*N*	Study type	Skin type	Settings	Results	Complications	Device	Fractionated
					more than double the fluence				
Kauvar et al. [85]	All colors—black, green, red, purple, blue, yellow, orange	39	Prosp OLT	N/A	1–10 treatments performed at 4–8-week intervals 56% used topical numbing, 32% used injection lido 2–6 mm spot 1064 and 532 nm 1,064–0.7-8.5 J 532–0.3-1.9 J	Analysis based on 36 tattoos that received 3 treatments: 86% showed at least 50% clearance 8%—>95% 22%—75–94% 56%—50–74% After 3 treatments—28% achieved 75–100% clearance After 6 treatments—66% achieved 75–100% clearance After 10 treatments—92% achieved 75–100% clearance After 6 treatments—66% achieved 75–100% clearance	5% adverse event rate including mild to mod pruritus, mild textural change, mild soreness, prolonged erythema, mild hyperpigmentation No scarring	Picoway	N
'Lorgeau et al. [86]	Ps vs. ns, all colors	49	Single-blind split tattoo RCT	II–V	Picoway: 1064 nm 450 ps; 532 nm 375 ps; 2–5.5 J Enlighten: 1064 nm 750 ps; 532 nm 750 ps; 2–8.4 J Versapulse: 1064/532 nm 5 ns; 2–8.4 J	Picosecond device superior to nanosecond device in clearance after 1, 2, and 3 treatments for black ink	Pain slightly less with ps, not significant	Picoway Enlighten Versapulse	N
Zhang et al. [87]	Ps vs. ns, black eyeliner tattoo	72	Retro review	IV (Chinese)	755 nm 750 ps 2.65 mm spot 3.75 J vs. 1064 nm 5–20 ns 3 mm spot 3.87 J 32 treated with ns Nd:YAG 40 treated with ps Alex 1–4 treatments	No significant difference noted—but wavelength is different	None	Picosure vs. Medlite C6	N
Eggenschwiler [88]	Qs and ps for iron infusion tattoo	13	Retro review	II–IV	Combination treatment with variable combinations	8 of 13 patients achieved complete removal	Persistent focal hypopigmentation occurred in 46.2%—not stratified based on	Unknown	N

(*Continued*)

TABLE 6. (*Continued*)

Author/date	Lesion	*N*	Study type	Skin type	Settings	Results	Complications	Device	Fractionated
					of qs YAG, ruby, ps YAG, ps 660 nm	Of these 8, between 4 and 9 laser sessions at 6–14-week intervals was required No patients were treated only with ps laser	type of laser used		
Kato et al. [89]	Combo pico + nano	42	Retro review	III–IV	1064 nm 2 ns/750 ps Started out with 3–4 treatment sessions using 2 ns pulse duration and then continued with 3–4 treatment sessions using 750 ps Compared clearance with predicted clearance per Kirby Desai score	Number of laser treatments needed was significantly smaller than what the Kirby Desai scale would predict Scanning electron microscopy revealed greater dispersion of ink particles with 750 ps vs. 2 ns	None	Enlighten	N

TABLE 7. Summary and Recommendations

Indication	Level of evidence	Recommendation
Nevus of Ota	Level 1b	Picosecond laser may be considered a first-line treatment option for Nevus of Ota and Hori's macules. Solar lentigines and freckles also tend to respond with a high degree of safety and efficacy. Café au lait macules may respond favorably. Other benign pigmentary conditions may have variable response.
Hori's macules	Level 1b	
Solar lentigines	Level 2b	
Freckles	Level 2b	
Café au lait macules	Level 3c	
All other benign pigmentary conditions	Level 4	
Rejuvenation	Level 2a	Picosecond laser is a good therapeutic option for photorejuvenation, particularly in skin of color where laser options may be more limited. Both unfractionated and fractionated delivery modes should be exploited to achieve optimal results.
Melasma	Level 2b	Picosecond laser may be considered as an adjunctive treatment option in combination with photoprotection, topical bleaching agents, and possibly other laser and systemic therapies for highly motivated patients with moderate to severe melasma who may also benefit from the concurrent reduction of benign pigmentation and photodamage.
Acne scars	Level 2b	Fractionated picosecond laser should be positioned as a treatment option for patients with mild to moderate acne scarring who desire minimal downtime and have perhaps failed other more well-established treatments. Acne scar patients who are skin of color and/or who present with concurrent pigmentary issues may also be selective candidates for fractionated picosecond laser. Striae alba can be treated with fractionated picosecond laser, but improvements tend to be modest. Fractionated picosecond laser may be considered as an adjunctive treatment modality in combination with other therapies for hypertrophic and atrophic surgical/traumatic scars.
Striae alba	Level 2b	
Atrophic and hypertrophic surgical scars	Level 3c	
Tattoo removal	Level 1a	Picosecond laser currently represents the gold standard treatment option for the removal of unwanted tattoos of almost any color.

97% good to excellent resolution rating compared with 46% from the nanosecond laser; and 93% satisfied to very satisfied patient satisfaction rating versus 40%, respectively. The picosecond laser was also associated with slightly less pain and less healing time. The rate of PIH with the picosecond laser was significantly reduced as compared with the nanosecond counterpart, although the absolute rates with both treatment modalities were relatively high (28% vs. 54%) [93].

Other Non-Melasma Pigmented Conditions

The successful treatment of other non-melasma pigmented conditions has been mostly limited to single case reports and small case series. The conditions that have been reported to respond favorably to picosecond laser by multiple separate sources include argyria (four case reports), minocycline hyperpigmentation (three case reports and a small case series), and infraorbital dark circles (one case report and one prospective open-label trial). Although these reports cast an optimistic outlook on the expanded use of picosecond lasers, further evidence is required in order to draw reliable conclusions. That being said, it is worthwhile noting that some traditionally difficult conditions to treat, such as minocycline-induced hyperpigmentation and chronic venous stasis hyperpigmentation have shown promising response and the use of picosecond laser in these settings should be considered an alternative treatment option when other modalities have proven unsatisfactory [30–39,41–45,94].

Comparative Studies and Controversies

Nevus of Ota, Hori's macules, solar lentigines in Asians, and freckles in Chinese have been the subject of picosecond versus nanosecond laser comparison trials

[23,24,28,93]. Ge et al. [28] conducted a randomized, double-blind, split lesion clinical trial comparing a 750 picoseconds alexandrite laser with a 70 nanoseconds alexandrite laser for the treatment of Nevus of Ota. In this study, 56 patients received up to six treatments that were delivered at 12-week intervals with a final 3-month follow-up evaluation. In both clinical clearance rates and subject satisfaction, the picosecond alexandrite laser outperformed the nanosecond counterpart. As noted above, Hori's macules also seemed to respond better to picosecond alexandrite laser [93]. Comparative trials between picosecond and nanosecond laser for the treatment of solar lentigines and freckles have been less clear. Vachiramon et al. [24] compared a 532 nm Nd:YAG picosecond laser with a pulse duration of 375 picoseconds with a 532 nm Nd:YAG nanosecond laser with a pulse duration of 5 nanoseconds in a split-body clinical trial for solar lentigines. Two lentigines per subject were randomized to receive a single treatment with either modality and then evaluated at a 12-week follow-up time point. Both treatments were performed at settings that induced clinical whitening of the lesions. A spot size of 3 mm remained constant, but the nanosecond laser was used at more than double the fluence of the picosecond laser. Investigator evaluation detected no significant differences in treatment efficacy. Subjects rated the PS-treated lesions as having 60.7% excellent response versus 32.1% for the NS-treated lesions, but this difference did not reach statistical significance. Subjects reported a statistically significant greater satisfaction level with the PS-treated lesions. There were no differences in healing time or adverse events, and both treatment modalities resulted in a 7.1% PIH rate. These data are ambiguous as subjects reported a greater satisfaction level with the PS-treated lesions, but objective clinical evaluation detected no differences. Interestingly, only two lesions per subject were chosen for treatment. Treating a greater number of lesions may result in more robust data and a clearer signal. Finally, Yang et al. [23] reported no differences between a picosecond and nanosecond alexandrite laser for the treatment of Chinese freckles. Both lasers performed excellently after a single treatment and a 2-month follow-up evaluation. There were also no reported differences in side effects and downtime. In the author's clinical experience, simple freckles tend to respond well to a large variety of short- and long-pulsed laser and light modalities making the sensitivity of this experimental model suboptimal to distinguish differences, if any, between picosecond and nanosecond laser.

Bottom Line

Picosecond laser is currently the United States Food and Drug Administration (FDA) cleared for the treatment of benign pigmented lesions. The accumulated evidence to date suggests that picosecond laser is a safe and effective treatment option for this indication across a wide spectrum of lesions and skin types. Comparative studies utilizing clinical, histological, and microscopic endpoints further suggest that picosecond laser may be safer and more effective than nanosecond laser in some situations, with potentially reduced risk of inducing post-inflammatory hyperpigmentation. This increased safety level may be due to the reduction of non-specific photothermal damage of the melanocyte and dermal–epidermal junction. While dermal lesions appear to clearly respond better to picosecond laser versus nanosecond laser, some of the comparative clinical data thus far remains ambiguous with regards to epidermal lesions. In the author's experience (DCW), the advantages of using picosecond laser for benign pigmented lesions becomes clearest at sub-500 picoseconds domains and relies heavily on achieving a highly sensitive and specific clinical endpoint—something that is sometimes more difficult to achieve with nanosecond devices. Optimization of these treatment settings and endpoints requires further study and additional data is required to truly define the precise risk of post-inflammatory hyperpigmentation with picosecond laser stratified by skin type. Additionally, more robust clinical comparative data with a focus on shorter pulse durations and refined clinical endpoints is still needed to further distinguish the differences between picosecond and nanosecond laser for the treatment of some benign pigmented lesions.

Level of Evidence

Nevus of Ota:	Level 1b
Hori's macules:	Level 1b
Solar lentigines:	Level 2b
Freckles:	Level 2b
Café au lait macules:	Level 3c
All other benign pigmentary conditions:	Level 4

Recommendation

Picosecond laser may be considered a first-line treatment option for Nevus of Ota and Hori's macules. Solar lentigines and freckles also tend to respond with a high degree of safety and efficacy, although superiority over nanosecond laser is less clear. CALM may respond favorably. Other benign pigmentary conditions may have variable response.

Rejuvenation

Seven prospective open-label trials and three split-face comparison trials involving a cumulative 200 patients have reported the use of picosecond laser for photorejuvenation of the face, chest, and extremities [46–55]. The first study was conducted in the setting of photodamaged chest and utilized a novel diffractive lens array, which allowed for the fractionation of a picosecond alexandrite laser [46]. This array consists of approximately 120 closely packed diffractive lenses that redistribute energy into peaks of high fluence on a background of very low fluence, thus mimicking a distribution pattern similar to that seen with traditional fractional laser. The high

fluence peaks deliver 20 times greater energy as compared with the low fluence background. Wu et al. treated 20 patients with skin types I–IV utilizing this system. Patients received 2–4 treatment sessions at 3-week intervals with a fixed 6×6 mm spot size, 0.71 J/cm^2, 750 picoseconds pulse duration, 2–4 passes for a total of $6{,}631 \pm 1{,}915$ pulses per treatment session. Both investigator and subject-reported outcomes were measured at 1 and 3 months after the final treatment session. These data demonstrated significant clinical improvements in dyspigmentation, skin texture, keratosis, and rhytids. Erythema remained unchanged from baseline. The majority of patients reported satisfaction with treatment results and downtime was reported as mild. These data were confirmed in a subsequent study of similar design, which included both chest and hands [49]. Utilizing the same diffractive lens array, Weiss et al. [50] treated 40 patients with peri-ocular and perioral rhytids. Four monthly treatments were delivered at a fixed 6×6 mm spot size, 0.71 J/cm^2, 750 picoseconds pulse duration, and 4 passes for a total of 5,000 pulses to the full face. Six patients underwent 2 mm punch biopsies of the peri-ocular skin at baseline, 1, 3, and 6 months post-treatment. The results showed significant improvement in Fitzpatrick–Goldman Wrinkle Scale at the 6-month follow-up time point. Furthermore, moderate to marked improvement was noted in facial dyschromia. Facial erythema did not significantly improve. Serial histological analysis revealed a steady increase in both collagen and elastic fibers throughout the dermis with a peak effect seen at the 6-month mark. Ge et al. studied 10 Chinese women with a split-face, non-randomized, evaluator-blinded clinical trial and found that treatment with the fractionated picosecond alexandrite laser resulted in significant improvements in wrinkling and global photoaging compared with untreated facial halves after four treatment sessions at 2-week intervals [47]. This study utilized a slightly stronger experimental design as opposed to a simple prospective, open-label trial and also utilized a lower fluence 8 mm optic for the treatment of skin types IV. Utilizing an alternative laser system, Berstein et al. examined the effects of a frequency-doubled 1064/532 nm picosecond Nd:YAG laser on facial photoaging [51]. This laser system delivers fractionated energy via a holographic beam splitter rather than a diffractive lens array. The 101 laser microbeams with a diameter of 150 μm are arranged in a uniform 10×10 grid pattern within a 6 mm spot size. Each pulse delivers approximately 5% density. In this study, 14 patients were treated with 1064 nm, 6 mm spot size, 450 picoseconds pulse duration, and energy of 1.3–2.5 mJ/microbeam. Five treatments were delivered at monthly intervals. An additional 10 subjects received treatment with 532 nm, 6 mm spot size, 375 picoseconds pulse duration, and energy of 1–1.4 mJ/microbeam. This cohort received four treatments at monthly intervals. Blinded evaluators rated 56.9% of subjects across both cohorts as having greater than 20% improvement. Subject satisfaction levels were high. Interestingly, although side effects and recovery time was reported as minimal in both cohorts and consistent with previous reports using fractionated picosecond laser, the subjects treated with the 532 nm wavelength seemed to experience a slightly elevated level of treatment pain and subsequent downtime. No significant differences in the clinical results were detected between the two treatment groups.

Comparative Studies and Controversies

Two studies have been conducted comparing the safety, tolerability, and efficacy of fractionated picosecond laser with 1927 nm fractionated thulium fiber laser for facial photorejuvenation, and one study has compared fractionated picosecond Nd:YAG versus unfractionated long-pulsed Nd:YAG [52,55] [Wu et al., submitted]. In the first comparative study, 20 subjects were randomized to receive either two fractionated thulium fiber laser treatments spaced 6 weeks apart or four fractionated and unfractionated picosecond alexandrite laser treatments spaced 3 weeks apart. The results demonstrated superior clinical performance of the picosecond alexandrite laser at a 12-week evaluation time point with an equivalent side effect profile [52]. Several factors detracted from the objective comparability in this study including the uneven treatment numbers, the use of both fractionated and unfractionated picosecond laser versus purely fractionated thulium fiber laser, relatively short follow-up evaluation time point, and the lack of detailed comparison of laser recovery time. In the second study, a randomized, split-face, double-blind design was utilized to compare a frequency-doubled 1064/532 nm picosecond Nd:YAG laser versus a fractionated 1927 nm thulium fiber laser [Wu et al., submitted]. Facial halves were randomized to receive either one of the two treatment modalities and three treatments at 1-month interval were delivered for both. Statistically significant improvement in photoaging parameters at 1, 3, and 6 months post-treatment was detected on both sides, but no statistical difference between sides was detected. In this study, subjects were asked to rate their recovery period quantitatively through daily dairies measuring degrees of redness, swelling, crusting, peeling, itch, and pain for the 14 days post-treatment. The aggregated scores over all treatments revealed significantly less redness, swelling, peeling, crusting, and itch associated with the picosecond laser-treated side at various time points. Finally, Yim et al. compared a 450 picoseconds 1064 nm fractionated Nd:YAG laser (PSYAG) with a 300 microseconds 1064 nm unfractionated Nd:YAG laser (LPYAG) in a split-face trial for photorejuvenation [55]. The randomized facial halves of 25 subjects received five treatments at 2-week intervals and final evaluations were performed 12 weeks after the final treatment session. Both lasers were used at 8 mm spot size and 1,500 pulses per treatment. The fluence for the PSYAG was 0.6–0.8 J/cm^2 compared with 4 J/cm^2 with the LPYAG. Using a 5-point scale, blinded investigators observed significantly greater improvement in visible pores at the lateral canthal region with PSYAG treatment versus LPYAG (54.2% vs. 41.7%, $P < 0.05$) but no

significant difference was detected in wrinkling. However, using 3D digital skin analysis (Antera 3D; MIRAVEX Ltd., Dublin) both wrinkles and pore size demonstrated significantly greater improvement with PSYAG treatment versus LPYAG (16.4% vs. 0.5% $P = 0.01$ and 41.3% vs. 3.9% $P = 0.048$, respectively). Interestingly, this study reported a significantly greater pain level on the PSYAG side during treatment. A potential drawback of this study was that it compared fractionated laser (PSYAG) versus non-fractionated laser (LPYAG).

Bottom Line

Fractionated picosecond laser is current U.S. FDA cleared for wrinkle reduction and the evidence to date demonstrates that it is becoming increasingly well-established as a useful tool for general photorejuvenation. The studies show a high level of safety associated with a moderate level of efficacy. Indeed, when compared with traditional non-ablative fractional laser, fractionated picosecond laser may have an improved side effect profile without sacrificing treatment efficacy [Wu et al. submitted]. This could be due to the unique mechanism of action of fractionated picosecond laser, which results in greater confinement of tissue injury to focal and precise points within the epidermis and papillary dermis [4]. Further study is required to refine the optimal treatment parameters for fractionated picosecond laser in regards to pulse energy, treatment density, and wavelength. Aside from the ultrashort pulse durations, one unique feature of currently commercially available picosecond lasers is the ability to deliver both non-fractionated and fractionated energy. For photorejuvenative purposes, and as suggested by the data from one of the comparative trials above, this dual capability has the potential to be leveraged for significant clinical advantage by being able to optimally target both discrete lesions as well as overall cutaneous elastosis with a single device. Further exploration of this concept is required.

Level of Evidence

Level 2a

Recommendation

Picosecond laser is a good therapeutic option for photorejuvenation, particularly in skin of color where laser options may be more limited due to adverse effect profile. Both unfractionated and fractionated delivery modes should be exploited to achieve optimal results.

Melasma

Melasma is a benign pigmentary condition that typically affects the face in characteristic distribution patterns. Risk factors associated with the development of melasma include genetic predisposition, hormonal influences, and ultraviolet radiation exposure. There is currently no known cure for this condition and the mainstays of treatment include topical bleaching agents and sun-protective regimens [95].

The use of laser for the treatment of melasma has a controversial history. Although previous reports with a variety of fractionated and non-fractionated modalities have shown limited success, the risks of rapid recurrence, rebound hyperpigmentation, and developing mottled hypopigmentation are significant. To date, picosecond laser has been used to treat melasma in one case series; one prospective open-label trial; four prospective, randomized, split-face trials; and one randomized controlled trial involving a cumulative total of 140 patients [56–62]. Choi et al. [57] conducted a randomized single-blind split-face clinical trial involving 39 patients with melasma. Facial halves were randomly assigned to either 2% hydroquinone control or non-fractionated dual-wavelength 1064/595 nm picosecond laser treatment. The treatment settings for the 1064 nm wavelength were 7–10 mm spot size, 0.2–1.5 J/cm^2, and 2–4 passes whereas the 595 nm wavelength was utilized at 5 mm spot size, 0.1–0.55 J/cm^2, and 1–2 passes. Both wavelengths had a pulse duration of 750 picoseconds. Five treatment sessions were conducted at 1-week intervals and patients were followed for 3 months after their final treatment. The investigators reported significantly better improvement in colorimeter assessment on the laser-treated side versus control, but the MASI score was only significantly better for the first week after treatment. No incidence of PIH or rebound was reported. In a second prospective, randomized, split-face clinical trial, Chalermchai et al. [58] utilized a fractionated picosecond Nd:YAG laser at 1064 nm wavelength and 450 picoseconds pulse duration to treat facial halves versus 4% hydroquinone control. The treatment parameters involved a 6×6 mm holographic beam splitter that delivered 1.3–1.5 mJ/microbeam for a total of 400–1,000 pulses for an estimated 8–12% density and an endpoint of mild erythema. Three treatments were delivered at 4-week intervals. The primary clinical evaluation was modified MASI score 4 weeks after the final treatment session. The investigators also evaluated melanin index, global satisfaction, DLQI, and adverse effects. The results demonstrated significantly greater improvement in modified MASI score on the laser-treated facial halves versus the control, although the absolute difference was relatively small (3.52 ± 1.4 vs. 4.18 ± 2.0). No significant differences were reported in melanin index and patient satisfaction.

Comparative Studies and Controversies

Additional studies have compared modified Kligman triple combination cream and nanosecond Nd:YAG (QSYAG) against picosecond alexandrite laser (PSAL) with or without diffractive lens array respectively [59,60]. In the first comparison, Wang et al. randomized three groups of subjects to receive either three treatments of fractionated PSAL at 4-week intervals (Group A), five treatments of fractionated PSAL at 4-week intervals (Group A2), or triple combination cream consisting of 0.01% fluocinonide acetonide, 4% hydroquinone, and 0.05% tretinoin applied nightly for 8 weeks, then twice weekly for 6 weeks, then once weekly for 6 weeks (Group

B) [60]. The investigators reported significant improvements in MASI score in all groups at the final evaluation time point which was set at 1 month following the final treatments for group A2 (3 months following the final treatments for group A1). However, no significant differences between the groups were detected. Laser-treated subjects appeared to have some improvement in spots, pores, and wrinkles via Canfield VISIA photographic analysis. No patients experienced recurrence or rebound for the duration of the trial. Lee et al. [59] compared PSAL with QSYAG in a randomized split-face trial involving 12 patients. Four treatments were delivered at 1-month intervals and subjects were evaluated at 3 months after the final treatment session. The PSAL was non-fractionated at a pulse duration of 650 picoseconds, 4.4–5.1 mm spot size, 0.88–1.18 J/cm^2, 3 passes and 1,000 pulses per treatment. The QSYAG was at 5 nanoseconds pulse duration and 1 pass each of the following settings were used: 8 mm spot, 2 J/cm^2; 6 mm spot, 3.5 J/cm^2; and 4 mm spot, 3.2 J/cm^2. All treatments were performed to an endpoint of mild erythema with edema but no petechiae. At the 3-month mark, pigment clearance was faster and significantly better on the PSAL treated side by both investigator and subject-reported outcomes. No unexpected adverse events were noted and there was no rebound pigmentation.

Bottom Line

To date, the clinical data on picosecond laser for the treatment of melasma remains mixed and unclear. Most studies have been hampered by suboptimal experimental design, modest clinical results and/or short follow-up time periods. Therefore, at this point, picosecond laser should not be used as monotherapy for melasma. However, it may be an effective adjunctive treatment option in combination with rigorous photoprotection, topical melanin inhibitors, and potentially other laser or systemic therapies as dictated by clinical circumstance. Several important clinical questions remain unanswered including the safety and efficacy of fractionated versus non-fractionated delivery, optimal treatment settings and endpoints, duration of disease improvement, risk of rebound, and the role of combination treatments with other therapeutic modalities.

Level of Evidence

Level 2b

Recommendation

Picosecond laser may be considered as an adjunctive treatment option in combination with photoprotection, topical bleaching agents, and possibly other laser and systemic therapies for highly motivated patients with moderate to severe melasma who may also benefit from the concurrent reduction of benign pigmentation and photodamage.

Scars

Picosecond laser for acne scars has been studied in one case series; four retrospective reviews; five prospective open-label clinical trials; and one randomized, split-face, comparison trial versus fractional 1550 nm erbium fiber laser involving a cumulative total of 194 subjects [8,9,63,65,66,71,72]. Additionally, there has been one case series of 16 patients studying picosecond laser treatment of hyperpigmented scars; one retrospective review of 24 patients with hypertrophic scars; one retrospective review of nine patients with atrophic surgical scars which was subsequently extended by the same group to include an additional eight subjects with atrophic scars and eight subjects with hypertrophic surgical scars; and one randomized, evaluator-blinded, split-body comparison trial of fractionated picosecond Nd:YAG laser versus 1565 nm fractional non-ablative laser for the treatment of striae alba in 20 subjects [64,67–70].

Acne Scars

In the first study, Brauer et al. [9] utilized the picosecond alexandrite laser with diffractive lens array to treat 20 subjects with skin types I–V. Six treatments at 4–8-week intervals with a 6 mm spot size, 0.71 J/cm^2, 750 picoseconds pulse duration, and an average of 3,072 pulses per treatment were administered. Subjects were then evaluated 3 months after the final treatment session. Scar volume was measured utilizing a three-dimensional imaging system. Biopsies at baseline and 3 months were taken for routine histological analysis. The results revealed a mean scar volume reduction of 27% at 3 months. Blinded evaluators reported an improvement of 1.4 on a scale of 0-4. Histological analysis revealed dermal changes consisting of an elongation and increased density of elastic fibers, an increase in collagen III expression, and an increase in mucin deposition over baseline. The investigators also noted that appreciable improvements were seen in texture and pigmentation, although these parameters were not formally measured as part of this experimental design. The second study on acne scarring utilized the picosecond frequency-doubled 1064/532 nm Nd:YAG laser with holographic beam splitter [8]. Twenty-one subjects with skin type II–V were treated with 1064 nm at 6 mm spot size, 450 picoseconds pulse duration, 1.3–2.8 mJ/microbeam energy, and 2 passes for a total of four treatment sessions at monthly intervals. An additional 10 patients with skin types II–V were treated in similar fashion but with 532 nm, 6 mm spot size and 1.1–1.5 mJ/microbeam energy. Evaluations were performed at the 12-week follow-up timepoint. The investigators reported that 81% of subjects showed some improvement, 48% showed >20% improvement, and 26% showed >30% improvement. On a 0-10 scale, mean improvement was scored at 1.4 with no significant differences between treatment groups. Subjects reported high satisfaction rates. All laser-induced side effects such as erythema and edema resolved within a few hours to up to 4 days post-treatment according to subject daily diaries.

Subsequent prospective open-label trials confirmed the above efficacy in ethnic populations using different metrics such as the Echelle d'Evaluation Clinique des Cicatrices d'acne (ECCA) scale and/or different laser devices [63,66].

Other Scar Types

The evaluation of picosecond laser for non-acne scars has been limited to case series and retrospective reviews. Reliable conclusions are therefore more difficult to arrive upon. Fractionated 1064 nm picosecond Nd:YAG laser showed promise for the treatment of hyperpigmented scars resulting from burn injury, road accident, leishmaniasis, and surgical procedure in a small case series of 16 patients [67]. Although the level of evidence is weak, there is likely an effective role for fractionated picosecond laser for the improvement of hyperpigmented scars given its more robust track record for the treatment of hyperpigmentation due to other causes such as benign pigmentary conditions and photodamage. Retrospective reviews of atrophic and hypertrophic surgical scar treatments with fractionated picosecond Nd:YAG laser have also demonstrated benefit. Interestingly, reflectance confocal microscopy of treated scars at the 6-month time point post-treatment revealed a net-like reconfiguration of collagen fibers and a significant reduction of epidermal thickness in hypertrophic scars compared to baseline [69,70]. Once again, more robust studies are required to further evaluate these findings.

Striae alba was studied in a randomized, double-blind, split-abdomen comparison trial between 1064/532 nm frequency-doubled picosecond Nd:YAG laser and 1565 nm erbium:glass non-ablative fractional laser in 20 subjects [64]. Three treatments were delivered at 3-week intervals and clinical evaluation was performed at 6 months post-final treatment. A modest improvement in striae texture and atrophy was reported for both treatment groups, with no significant differences detected. Striae density was not significantly improved by either treatment modality. Subjects rated their improvement between 45 and 50% on both sides. The picosecond laser was rated as less painful in all three treatment sessions, although this difference was only statistically significant for treatments 1 and 2. Similarly, the picosecond treatment was associated with faster healing time after each treatment, but the difference reached statistical significance only after treatment 2. Unfortunately, no histological specimens were analyzed in this study and so no further insight could be provided.

Comparative Studies and Controversies

There has been one randomized, single-blind, internally controlled split-face comparison trial between fractionated 1064 nm picosecond Nd:YAG laser and 1550 nm erbium:fiber non-ablative fractional laser [65]. The facial halves of 30 subjects were randomized to receive either picosecond laser or Er:fiber laser for four treatments at 4-week intervals, with final evaluations performed 4 and 8 weeks later. Using the ECCA scale, blinded evaluators reported roughly 30–40% improvement on both sides with no significant differences detected. Similarly, subject-reported improvement and satisfaction was equivalent for both sides. The Canfield Visia (Canfield Imaging Systems, Fairfield, NJ) digital imaging system was used to assess changes in pore size. Both treatment modalities resulted in a significant improvement, but the Er:fiber laser achieved significantly more improvement as compared with the picosecond laser. Most side effects were found to be equivalent between the two treatment halves, but the picosecond side was associated with significantly greater immediate pinpoint bleeding and the Er:fiber side had significantly greater pain. It is difficult to make strong recommendations based on a single comparative trial, but the general equivalence between fractionated picosecond laser and traditional non-ablative fractional laser seems in keeping with other comparative trials studying different indications [52] [Wu et al., submitted]. However, it is important to note that the follow-up period of 8 weeks in the Chayavichitsilp et al. study above is somewhat short and a more accurate assessment of acne scar response is typically seen at 3–6 months following treatment.

Bottom Line

Fractionated picosecond laser is currently U.S. FDA cleared for the treatment of acne scars. The current evidence demonstrates a high level of safety and tolerability associated with a moderate level of efficacy. However, robust and rigorous clinical trial data remains relatively sparse. Encouragingly, reports thus far seem to suggest that the risk of post-inflammatory pigmentary alteration is low when using fractionated picosecond laser which has added significance due to the high prevalence of acne scarring in skin of color. There are several unmet needs in the current literature including the optimization of treatment settings, stratification based on acne scar type, more rigorously designed clinical trials with validated endpoint evaluation metrics, comparative trials, and exploration of potential combination strategies with other established therapeutic modalities.

Level of Evidence

Acne scars	Level 2b
Striae alba	Level 2b
Hypertrophic and atrophic surgical scars	Level 3c

Recommendation

Fractionated picosecond laser should be positioned as a treatment option for patients with mild to moderate acne scarring who desire minimal downtime and have perhaps failed other more well-established treatments. Acne scar patients who are skin of color and/or who present with concurrent pigmentary issues may also be selective candidates for fractionated picosecond laser. Striae alba can be treated with fractionated picosecond laser, but improvements tend to be modest. Fractionated picosecond laser may be considered as an adjunctive treatment

modality in combination with other therapies for hypertrophic and atrophic surgical/traumatic scars.

Tattoo Removal

Tattoo removal is the oldest and most established dermatologic indication for picosecond laser. It was first reported in the dermatologic literature at the turn of the century where it was utilized in a pre-clinical and experimental fashion for the removal of unwanted tattoos [73,74]. Predicated on the theory of selective photothermolysis [1], the size of tattoo ink particles suggested that a picosecond pulse duration would be required to optimally target and remove them [75]. To test this hypothesis, Ross et al. [73] compared a 35 picoseconds versus 10 nanoseconds 1064 nm Nd:YAG laser for the removal of black tattoos in 16 patients [73]. The results clearly demonstrated the superiority of the picosecond pulse. Subsequently, a 500 picoseconds 795 nm titanium sapphire laser was compared with a 50 nanoseconds 755 nm alexandrite for black tattoo removal in a guinea pig model [74]. Once again, the picosecond pulse significantly outperformed the nanosecond pulse. Currently, lasers with true picosecond pulse durations have been developed at wavelengths of 532, 730, 755, 785, and 1064 nm and have all been reported as effective at clearing almost every color of tattoo ink as well as paradoxical darkening of tattoo [77,79–82,85,96]. A systematic review was published in 2016 analyzing the safety and efficacy of picosecond lasers for tattoo removal, and the general consensus is that they work very well and have a high degree of safety and tolerability [97,98].

Comparative Studies and Controversies

Although shorter pulse durations are advantageous from both a conceptual and scientific standpoint, there remains some controversy regarding the continued role of nanosecond pulse durations for optimal tattoo removal [99]. Three comparative clinical trials consisting of two prospective, single-blind, randomized, split tattoo designs and one retrospective review have studied nanosecond laser versus picosecond laser where both devices were attempted to be used at optimal settings [84,86,87]. The first split tattoo study was conducted by Pinto et al. and compared a 5 nanoseconds pulsed 1064 nm Nd:YAG laser versus a 450 picoseconds pulsed 1064 nm Nd:YAG laser for the treatment of black tattoos. After two treatment sessions, the investigators found no statistical difference in efficacy although the picosecond laser was significantly less painful [84]. The second split tattoo study reported the opposite effect, with picosecond Nd:YAG lasers with pulse durations between 450 and 750 picoseconds performing superiorly to their 5 nanoseconds pulsed nanosecond counterpart [86]. The final study was a retrospective review of eyeliner tattoo removal that not only differed in comparing picosecond versus nanosecond lasers but also different wavelengths of laser (picosecond 755 nm vs. nanosecond 1064 nm) even though the ink color to be removed remained a constant black [87]. This study demonstrated no difference in clinical efficacy, but due to the increased number of variables as well as the weaker study design, these data are difficult to interpret with clarity.

Upon closer inspection, the Pinto et al. study had design elements that call into question the investigators' final conclusions. First, only two treatment sessions were conducted. This short study duration raises potential problems because it is frequently the case that the initial tattoo treatment sessions yield the most dramatic results and so differences may be more difficult to detect. Additionally, as tattoo treatment progresses into the later stages, tattoo ink particle size diminishes, a fact that would theoretically increasingly favor a shorter pulse duration device. It, therefore, remains an open question as to whether or not the equality of the two treatment modalities would have remained if the treatment sessions were continued further. Furthermore, a review of the laser parameters used in this study reveals that the picosecond laser settings could have potentially been further optimized, and the nanosecond laser fluences were, on average, greater than double their picosecond counterparts. One interpretation of these findings is that the nanosecond device requires more than double the fluence to achieve the same clinical result as the picosecond device. Previous work has demonstrated that this elevated fluence requirement results in a demonstrable increase in non-specific tissue damage which may have clinical safety implications [26]. Alternatively, it could be argued that the picosecond laser settings could have been significantly increased without affecting safety or tolerability. Either way, these alternative hypotheses both suggest that the picosecond laser system has potential advantages over the nanosecond system that could not be appropriately explored and evaluated in this study design. Lorgeou et al. [86] performed the second split tattoo comparative clinical trial using greater patient numbers, greater treatment sessions, and including all colors and reported a statistically significant picosecond advantage in black ink removal (especially those that were professionally done) but no advantage for other colors. However, the actual absolute clinical difference in efficacy between the two lasers was modest and both treatment modalities appeared safe.

It has been theorized that longer nanosecond pulses and shorter picosecond pulses are *both* required to optimally target large and small tattoo particles respectively. In this scenario, the argument is that there is benefit to starting treatments at nanosecond pulses in order to target the initial large tattoo pigments before transitioning to the picosecond pulses as the tattoo particles become smaller. However, there seems to be little scientific or clinical evidence in support of this hypothesis to date and, on the contrary, past and present scientific and clinical studies have suggested that the need for nanosecond pulses in targeting larger tattoo particles is questionable. Kato et al. conducted a retrospective review comparing combination 2 nanoseconds and 750 picoseconds 1064 nm Nd:YAG laser versus 2 nanoseconds alone 1064 nm Nd:YAG laser for removal of black tattoo and concluded that the combination pulse was

superior [89]. Unfortunately, no picosecond alone group was included in the analysis, therefore, making it difficult to determine the true benefit of combining nanosecond and picosecond pulses. The investigators did conduct scanning electron microscopy analysis of samples treated with either 2 nanoseconds or 750 picoseconds pulses and these data revealed that the 750 picoseconds pulse irradiation consistently resulted in greater dispersion of tattoo particles regardless of original tattoo particle size. Similarly, two-photon microscopy analysis of *in vivo* tattoo ink irradiated with 5–10 nanoseconds versus 750 picoseconds laser has demonstrated that the picosecond pulses fragmented tattoo particles of all sizes with higher efficiency as compared to nanosecond pulses [100]. Only when the nanosecond laser fluences were elevated to greater than twice that of the picosecond laser, or when the picosecond laser was deliberately utilized at very low fluence was superiority demonstrated for the nanosecond pulses [100]. Finally, Ahn et al. [101] utilized an experimental model to directly compare the effect on tattoo particles of a 750 picoseconds 1064 nm Nd:YAG laser versus a 5 nanoseconds 1064 nm Nd:YAG laser. In this study, compelling data demonstrated that (i) at all equivalent fluence levels, the picosecond laser achieved a greater degree of particle fragmentation than the nanosecond laser; (ii) at low fluence levels, the picosecond laser remained effective whereas the nanosecond laser was unable to induce significant particle fragmentation; (iii) repeated picosecond exposures continued to fragment tattoo particles whereas repeated nanosecond exposures eventually became ineffective at targeting the smaller fragmentations; and (iv) when irradiated in sequence, picosecond exposure followed by picosecond exposure resulted in greater fragmentation as compared with nanosecond-then-nanosecond, nanosecond-then-picosecond, and picosecond-then-nanosecond. These data support the notion that nanosecond pulses may not be necessary for the optimization of tattoo removal.

Bottom Line

Picosecond laser is a safe and effective therapeutic modality for the removal of unwanted tattoo of almost any color and currently represents the gold standard. The accumulated scientific and clinical evidence to date concludes that the shorter pulse duration confers a distinct advantage when other laser parameters remain equal. The evidence also suggests that the shorter the pulse gets (within currently commercially available and tested devices), the greater becomes the efficacy for tattoo removal. There is no evidence to suggest that larger tattoo particles are more optimally targeted by longer nanosecond pulses. Conflicting reports in the literature can potentially be explained by study design variations and variable study device optimization. That being said, there still remains two practical clinical situations in which a nanosecond laser may outperform a picosecond laser: if the devices in question have vastly different limits in terms of power output and if the wavelengths of the two devices are different and not optimized for specific tattoo colors. High fluence nanosecond laser can potentially be more effective than low fluence picosecond laser for tattoo removal, although greater fluences will result in greater tissue damage. Additionally, the relationship between fluence and efficacy may be complex. For example, Izikson et al. [75] reported a *decreased* efficacy of high fluence picosecond laser compared to medium and low fluence for the removal of iron oxide tattoo in a Yorkshire pig model. This result could have simply been due to spot size variation (high, 1.3 mm spot; medium, 1.9 mm spot; and low, 2.9 mm spot) or the possibility that the high fluence picosecond laser exceeded tissue plasma formation threshold to a greater degree resulting in the quicker and more superficial formation of plasma that blocked further laser penetration. It is worthwhile to note that the original work by Ross et al. utilized an experimental laser with a pulse duration of 35 picoseconds and mathematical calculations have suggested that pulse durations of between 10 and 100 picoseconds may be optimal for tattoo particle targeting via the principles of selective photothermolysis [1,3,73,75]. Currently available picosecond lasers have pulse durations no shorter than 250 picoseconds. The future development of even shorter picosecond pulsed devices has the potential to demonstrate the advantages of this modality in a clearer fashion, shed light on whether pulse duration that are *too* short may even have a detrimental effect due to increased plasma formation, and may give rise to further indications and applications.

Level of evidence

Level 1a

Recommendation

Picosecond laser currently represents the gold standard treatment option for the removal of unwanted tattoos of almost any color.

CONCLUSION

The dermatologic applications of picosecond laser along with their associated levels of evidence and clinical recommendations are summarized in Table 7. Picosecond laser is an expanding field in dermatology. A per year analysis of Tables 1–6 reveals that the Level of Evidence associated with each major dermatologic indication continues to progress as clinical trials explore increasingly refined questions with increasingly rigorous experimental designs. Future directions may include the development of even shorter pulse durations, improvements in fractionation method and delivery, and exploration of the utility of pulsing other laser wavelengths in the picosecond (or shorter) domain. The introduction of newer devices along with continued improvements in clinical technique and experience will drive the refinement and expansion of this technology.

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