

REVIEW ARTICLE

Concomitant use of isotretinoin and lasers with implications for future guidelines: An updated systematic review

Fatima N. Mirza¹  | Humza N. Mirza² | Khalil A. Khatri³

¹Yale School of Medicine, Yale University, New Haven, Connecticut

²University of Michigan Medical School, University of Michigan, Ann Arbor, Michigan

³Skin & Laser Surgery Center of New England, Nashua, New Hampshire

Correspondence

Fatima N. Mirza, Yale School of Medicine, Yale University, New Haven, CT 06510.
Email: fatima.mirza@yale.edu

Abstract

It is generally believed that intervention on skin while on isotretinoin or within 6 to 12 months after treatment can lead to prolonged healing and abnormal scarring. The objective of this systematic review is to evaluate the body of evidence on concomitant use of isotretinoin and lasers for adverse events as a consequence of treatment. A PRISMA-compliant systematic review (Systematic Review Registration Number: CRD42017056492) of 12 electronic databases was conducted for the terms “laser” and “isotretinoin” or associated brand names from inception until June 2020. Subsequent reference search of studies meeting predefined inclusion criteria were conducted, and all articles were evaluated for bias and assigned levels of evidence to facilitate data synthesis. The search strategy produced 29 studies. Of 871 patients included in the studies of interest, 12 experienced transient adverse effects that resolved spontaneously, and only two presented with keloid formation, both from case reports. This systematic review suggests the risk associated with concomitant isotretinoin and laser use is small to absent. Further studies are needed, but these results suggest that current contraindications may be overly cautious.

KEYWORDS

concomitant treatment, isotretinoin, lasers, safe and effective, systematic review

1 | INTRODUCTION

The American Academy of Dermatology guidelines recommends delaying laser resurfacing 6 to 12 months after discontinuing isotretinoin, citing early case series describing delayed wound healing in patients with concomitant use. Current recommendations rely heavily on case reports published over three decades ago.

Acne is the most common skin condition in the United States, affecting up to 50 million American annually.¹ A subset of these patients suffer from severe inflammatory acne, often presenting with severe acne scars. There is evidence that early intervention results in better outcomes.^{2,3} Therefore, it is important to consider the impact on the patient when requesting delay of laser treatment due to guidelines developed from multiple-decade old case reports.

In 2017, two consensus statements considered several procedural interventions in the setting of isotretinoin, challenging the common

practice of a latency period between systemic isotretinoin therapy and other treatments. Since that time, several additional studies have been published with no systematic review considering the adverse consequences of concomitant laser and isotretinoin. Furthermore, these studies did not report the efficacy, frequency, nor dosage of the lasers; important metrics for understanding limitations of practical laser use in this context. Our aim was to conduct a systematic review that may inform evidence-based guidelines and shape clinic practice for the benefit of the patient, focusing specifically on laser use.

2 | METHODS

The protocol was registered on International Prospective Register of Systematic Reviews, and adheres to the principles of the PRISMA guidelines⁴ (CRD42017056492).

2.1 | Search strategy and study selection

We searched 12 databases for any published studies through June 2020 with the search strategy: ((laser* OR photodynamic*) AND (Isotretinoin OR Accutane OR Roaccutane OR Amnesteem OR Claravis OR Absorica OR Isotroin OR Epuris)[all]). No language restriction was applied, and inclusion/exclusion criteria were assessed (supplemental Table S1). We checked the bibliographies further potentially eligible studies. We used the Oxford Center for Evidence-Based Medicine Levels of Evidence⁵ to assign the appropriate value to facilitate data synthesis.

2.2 | Quality assessment

The Cochrane Methods Bias Group's Risk of Bias in Non-Randomized Studies - of Interventions (ROBINS-I) Tool⁶ was used to assess risk of bias in studies by two review authors, with disagreements resolved by a third author (supplemental Table S2).

2.3 | Data synthesis

Two researchers extracted data. The outcomes related to the review question considered the efficacy (eg, cosmetic improvement) or adverse events (eg, scarring, keloids) associated with concomitant use, and if a control group was provided, the comparison of these outcomes between groups.

3 | RESULTS

After an iterative process of cross referencing, 29 studies met the inclusion criteria (supplemental Figure 1).

The 29 retrieved studies include one expert opinion, eight case reports, 11 uncontrolled open-label trials, and eight controlled open-label trial, and included an aggregate of 871 patients (Table 1).

3.1 | Controlled open-label trials

One study considered the difference between patients undergoing isotretinoin and laser treatment with patients on prescription alone. Moradi et al¹⁴ enrolled 148 patients for laser resurfacing on oral isotretinoin for acne scarring. The intervention arm was treated with three Nlite and five weekly Er: YAG sessions whereas the age-matched control group received isotretinoin alone. At 6 months post-treatment, rates of post-inflammatory hyperpigmentation were the same between groups at 3%.

Two studies used a split-face model. Saluja et al²⁸ and Xia et al³⁰ conducted a randomized split-face control trial on 10 and 18 patients, respectively, for acne or acne with treatments with an erbium-doped laser. Patients showed improvement in scarring without adverse

effects, and for the latter, significantly improved comedo lesions on the non-ablative fractional laser (NAFL)-treated half-faces.

Five studies subjected all patients to laser treatment and compared a group with concomitant isotretinoin use with a control group not on isotretinoin. Leal and Cantu¹⁷ treated 60 patients for acne scarring with fractionated erbium laser on and off low-dose of isotretinoin; no difference or variation on the erythema, edema, and scabbing in the recovery process was observed. Kim et al²⁵ evaluated 20 patients on fractional ablative carbon dioxide laser treatment with moderate to much improved cosmetic scores, and erythema and crust associated with laser treatment in both groups resolved in all patients within 1 month. Chandrashekar et al²⁴ compared 60 patients treated with either carbon dioxide or 980 nm diode on isotretinoin (0.5 mg/kg); roughly 8% of those treated with carbon dioxide laser experienced hyperpigmentation that resolved within 2 months, and all report excellent results. Yoon et al²³ enrolled 35 participants who underwent acne scar revision with a 1550 nm erbium-doped laser, where 94% of the concomitant group showed improvement vs 88% of the control. No adverse events were reported. Kim et al³⁴ demonstrated the safe use of CO₂ laser therapy and fractional microneedle radiofrequency for acne and acne scarring in 43 patients compared to 28 patients not on isotretinoin. Those on concomitant treatment had improved scar global assessment scores, and no persistent side effects were observed.

3.2 | Uncontrolled open-label trials

Five studies focused on laser hair removal, four on acne scar revision, and three on a combination or other.

Khatri⁹ reported 810 nm diode laser hair removal on the axilla, bikini, and chin in seven female patients, and 1-month post-treatment, no scarring was found. One patient developed a transient bulla that resolved spontaneously within 1 month. Cassano et al¹⁰ presented six women undergoing laser hair removal on the face, where one patient presented with a sparse dotted crusting that healed spontaneously within a few days. Khatri and Garcia¹² described six female patients with satisfactory hair removal and no scarring during the 6 month follow-up. Khatri¹³ reviewed 11 patients who underwent laser hair with a 1064 nm Nd:YAG laser where one patient experienced transient hyperpigmentation that resolved within 3 months. This rate of complications was not higher than that observed with patients taking isotretinoin alone.

Hann et al¹⁵ used a 1550 nm infrared fractional laser to treat acne scarring in 35 patients. Using a five-point cosmetic scale, over 80% of patients demonstrated moderate to excellent improvement, and no hypertrophic scarring or keloids were found. Jeong et al²⁰ treated 20 patients on isotretinoin with a single session of full-face ablative fractional carbon dioxide laser. At four-year follow-up, and acne scar revision was deemed satisfactory. Khatri et al²⁶ tested three sites on a 19-year-old man's lower back with a nonablative fractional laser, an ablative fractional laser, and a full ablative laser on 40 mg twice daily isotretinoin for 4 months. Clinical assessment and a 4-mm punch biopsy was performed at each treatment site during the six-month follow-up visit. While the sites treated with fractional laser showed

TABLE 1 Results of systematic review on concomitant use of lasers and isotretinoin

References	Type of study	Study size	Patient request	Laser	Frequency (t = treatment, s = session)	Dosage	Control	Follow-up period	Efficacy	Adverse events	Level of evidence
7	CR	1	Rosacea	Argon, 1.3 W, 0.2 second	1 t	60 mg QD	Self	4 month		Keloid formation in keloid-prone patient	4
8	CR	1	Capillary Vascular Malformation	585 nm pulse dye, 6.0 J/cm ²	1 t	Unknown	Self	0.5 month		Keloid formation	4
9	PUOLT	7	LHR	810 nm diode, 80/90 W, 300 ms	\bar{x} = 5 t	20-80 mg QD		1 month	Satisfied hair removal	Transient bulla, resolved in 1 month	3
10	PUOLT	6	LHR	810 nm diode	4-9 seconds	0.3-0.5 mg/kg QD		Immediate	No cutaneous changes	Spontaneously healing sparse crusting	3
11	HUOLT	112	Facial Nevi (10), LHR (44), AS (53), Keloids (5)	quality-switched ruby, diode, intense pulsed ER: YAG, Nlite, pulsed dye	Variable	Variable		6 month		None	3
12	PUOLT	6	LHR	1200 nm pulser, 22-27 J/cm ² , 20 ms	\bar{x} = 4 t	40-80 mg QD		6 month	Satisfied hair removal	None	3
13	PUOLT	11	LHR	1064 nm Nd: YAG, 30-50 J/cm ² , 10-30 ms	\bar{x} = 12 t	0.5 mg/kg QD		Immediate	Rate of complications not increased when taking isotretinoin	Transient hyperpigmentation, resolved in 3 months	3
14	PCOLT	148	AS	(a) Nlite, 3 J/cm ² ; (b) ER: YAG, 0.6-0.7 J/cm ²	(a) 3 seconds and (b) 5 weekly s	1 mg/kg QD	Age-matched patients	6 month	Satisfied scar removal	Hyperpigmentation at equal rate (3%) in both groups.	2
15	PUOLT	35	AS	1550 nm infrared fractional	\bar{x} = 3 t	10 mg QD		Immediate	80% patients moderate-excellent improvement	Transient mild acneiform eruption	3
16	PUOLT	100	Various	Erbium, vascular, Q-switched alexandrite, 532 nm Q-switched, 1064 nm Nd: YAG, and non-ablative fractional	Variable	Variable		Up to 7 years	No hypertrophic scars or keloids		3
17	HCCT	60	AS	Fractionated erbium (50-70 μJ)	Variable	20 mg QD	Patients with acne scarring who had not taken isotretinoin during the study period		No difference in erythema, edema, and scabbing in recovery process between groups.		2

(Continues)

TABLE 1 (Continued)

References	Type of study	Study size	Patient request	Laser	Frequency (t = treatment, s = session)	Dosage	Control	Follow-up period	Efficacy	Adverse events	Level of evidence
18	EO		LHR and AS	Long-pulsed Nd-YAG laser and microfractional erbium glass	Variable	Variable	Patients undergoing the same treatments not on isotretinoin.	Up to 10 years	Erythema/perifollicular edema comparable. Acne scar resurfacing results better concomitant.		5
19	CR	1	Cutaneous Rosai-Dorfman Disease	pulsed dye		10 mg BID			Satisfactory clearance.		4
20	HUOLT	20	AS	Ablative fractional CO ₂	1 t	Variable		4 years	Satisfactory clearance.		3
21	CR	1	Multiple eccrine hydrocystomas	Ultrapulse CO ₂ , 800 W, 20-Hz, 0.3-msec	1 t	20 mg 6w		1 year	Improvement but eventual recurrence		5
22	CR	1	Sebaceous hyperplasia	CO ₂	2 t	150 mg/kg		2 years	Clearance		5
23	PCOLT	35	AS	1550 nm erbium-doped, 35-40 mJ, 8 passes	3-4 weeks for 2-6 seconds	10 mg QD	Patients with acne scarring who had not taken isotretinoin for at least 6 months	Immediate assessment after last session	94% concomitant showed improvement vs 88% controls		2
24	HCCT	60	AS (50) and LHR (10)	(a) CO ₂ ; (b) diode 980 nm hair removal	4 t every 6 weeks	0.5 mg/kg QD + topical medication	topical medication only	6 month	(a) Excellent scar revision; (b) Safe hair removal	(a) 8% patients transient hyperpigmentation, resolved 1-2 months; (b) none	2
25	HCCT	20	AS	CO ₂ , 30 W, 1 ms	1-6 seconds	10-40 mg/d QD	Patients who had not taken isotretinoin	48 month	Scar improvement	Erythema/ crust, resolved 1 month.	2

TABLE 1 (Continued)

References	Type of study	Study size	Patient request	Laser	Frequency (t = treatment, s = session)	Dosage	Control	Follow-up period	Efficacy	Adverse events	Level of evidence
26	PUOLT	1	AS	(a) Nonablative fractional (1540 nm, 100 mJ/mB, 3 passes); (b) ablative fractional laser (erbium:YAG 2940 nm, 91 J/cm ² , 3 passes); (c) full ablative (erbium:YAG 2940 nm, 2 J, 8 passes)	1 t	40 mg BID	None	6 month	Not reported	(a) None; (b) None; (c) Mild erythematous scar	3
27	PC	71	Hair Reduction or AS	(a) Long-pulsed Nd:YAG (1064 nm, 9 mm, 30 ms, 40 J/cm ²) (b) Fractional ER:YAG 2940 nm, long pulse or scanner (c) Fractional CO ₂ 30 mj,pulse 0.04 second, 100 pixel (d) Full face conventional CO ₂ resurfacing 3 mm spot, 500 Hz (e) Q-switched Nd:YAG 1.5 mm spot, 400mj	Varies	2-110 mg/kg	None	Varies	Not reported	(a) None (b) resolving post-inflammatory pigmentation (c-d) None (e) transient erythema	2
28	RSFCT	10	AS	Erbium doped 1550 nm NAFL	3 t 4 weeks apart	125-325 mg/kg	Split-face	4mo	50% moderate improvement, 10% significant improvement		2
29	CS	2	Nodulocystic Acne	10 600 nm CO ₂ fractional 38-42 mJ, 5.51 J/cm ²	1 t	0.05%	None	2-10mo	Significant improvement.	Transient hyperpigmentation, self-resolving	5
30	RSFCT	18	Acne	1550 nm Erbium: glass fractional (20 mJ/cm ² , 100-169 points per area)	Three treatments	10 mg QD	Split-face	Immediate	Comedo lesions significant improved in NAFL-treated half face.	Mild transient erythema	2
31	CR	1	Multiple eccrine hidrocystoma	Er:YAG (19 J, 2 mm spot size, 3 Hz)	Single session	20 mg QD	None	1 year	Successful treatment of lesions without recurrence.		1
32	PC	46	AAS	Nd:YAG	12 treatments, 2 week intervals	0.2-0.3 mg/kg/d	None	Immediate	Baseline improvement.		2
33	RUOLT	25	Recalcitrant Rosacea	595 nm Pulsed-dye (5-8 J/cm ²)	3 t	10 mg QD	None	4mo	Baseline improvement.		3

(Continues)

TABLE 1 (Continued)

References	Type of study	Study size	Patient request	Laser	Frequency (t = treatment, s = session)	Dosage	Control	Follow-up period	Efficacy	Adverse events	Level of evidence
34	ROS	71	AAS	Ablative fractional	Varies	Varies	Patients not on isotretinoin.	Varies	Scar decrease more pronounced on concomitant therapy.		3
35	CR	1	Lupus miliaris disseminatus faciei	595 nm pulsed dye 1.5 ms	6 seconds	10 mg QD	None	5mo	Effective treatment without recurrence.		1

Note: Type of Study, CR, Case Report; CS, Case Series; EO, Expert Opinion; HCCT, Historical Controlled Clinical Trial; PC, Prospective Cohort; PCOLT, Prospective Controlled Open-Labelled Trial; PUOLT, Prospective Uncontrolled Open-Labelled Trial; ROS, Retrospective Observational Study; RSFCT, Randomized Split-Face Controlled Trial; RUOLT, Retrospective Uncontrolled Open-Labelled Trial. Patient Request, AAS, Acne and Acne Scarring; AS, Acne Scarring; LHR, Laser Hair Removal.

normal appearing skin, the full ablative laser treatment site showed a mildly erythematous scar. However, researchers note the settings for this treatment site were "aggressive." Moradi et al¹¹ treated 112 patients on isotretinoin for facial nevi, hair removal, acne scarring, and keloids with one of seven lasers. During a six-month follow-up, no significant changes on wound healing, long-standing erythema, scars, and keloid formation were observed. Gold et al³² administered low-dose isotretinoin in combination with Nd:YAG laser treatments and found significant reduction in acne scarring without any complications.

Allisa et al in 2011¹⁶ enrolled 100 patients on isotretinoin therapy for treatment with erbium, vascular, Q-switched alexandrite, 532 nm Q-switched, 1064 nm Nd:YAG, and non-ablative fractional laser. No hypertrophic scars or keloid development was noted. Mahadevappa et al in 2016²⁷ treated 163 patients with fractional or full face CO₂, fractional Er:YAG, Q switched Nd YAG, long pulse Nd-YAG, or long pulsed diode lasers on concomitant isotretinoin for hair removal or acne scarring. Three patients exhibited transient erythema or pigmentation that resolved. Kwon et al³³ demonstrated statistically significant improvement from baseline of recalcitrant papulopustular rosacea with pulse dye laser, fractional microneedling, and concomitant isotretinoin without any adverse events.

3.3 | Case reports

Zachariae⁷ observed one woman with rosacea undergo two argon laser sessions with minor transient erosions. One month after starting 60 mg daily isotretinoin, she was treated in the same area and found that the lesions took more than 8 weeks to heal, and 4 weeks later she developed keloid scarring at these sites. A keloid on her left knee was found, indicating a tendency to form keloids. Bernestein and Geronemus⁸ reported a case of an Asian woman treated for a capillary vascular malformation of her neck with a 585 nm pulsed dye laser. After five treatments without adverse effects, she began isotretinoin and developed keloid scarring 2 weeks after her next treatment.

Han et al¹⁹ described a case of cutaneous Rosai-Dorfman Disease managed with 10 mg twice daily isotretinoin and pulsed dye laser treatment with no adverse events. Park et al²¹ treated a 57-year-old woman with multiple eccrine hidrocystoma with 20 mg daily isotretinoin followed by a single CO₂ laser session. Good effect was achieved, though eventually the lesion recurred. Similarly, Noh et al²² used two sessions of CO₂ laser and isotretinoin 150 mg/kg to clear previously laser-resistant sebaceous hyperplasia of the face, which responded well clinically without side effects or recurrence.

Pestoni et al²⁹ used concomitant tretinoin and fractional CO₂ laser on two patients for successful treatment of nodulocystic acne, resulting in improvement without significant adverse events. In addition, Demirhan et al³¹ used a single session of Er:YAG laser and isotretinoin to successfully treat multiple eccrine hidrocystoma without recurrence at 1 year. No adverse events were reported.

Ma et al³⁵ successfully use six sessions of 595 nm pulse-dye laser treatment with isotretinoin to treat lupus miliaris disseminatus faciei without side effects.

3.4 | Expert opinion

Patwardhan et al¹⁸ reported that their practice has been treating patients on isotretinoin concomitantly with the alexandrite laser for hair reduction for over a decade. Due to early case reports, lower fluencies were used on patients, but have since been modified to the same laser settings for both patients with and without a prescription for isotretinoin. The degree of erythema and perifollicular edema were comparable to those not on isotretinoin therapy. Patients are also treated with a Nd: YAG and microfractional erbium glass laser for acne scarring while on isotretinoin and the results have been comparable or superior to those patients not on oral isotretinoin.

4 | DISCUSSION

4.1 | Summary

Studies considering concomitant laser and isotretinoin use consisted of 871 patients, the highest collated to date on this topic. Of these, 587 sought acne scar revision and 84 sought laser hair removal. Fourteen experienced adverse effects^{7-10,13-15,24,26}; 12 of these were transient hyperpigmentation or eruptions resolving spontaneously. Three papers suggested that this was equal to the rate of complications in the control group (use of isotretinoin alone).^{14,24,25} Two demonstrated keloid scarring. Both of these patients were cited in case reports that fall among the lowest level of evidence of all studies and among these two, one patient was deemed "keloid-prone." This systematic review represents the largest cohort of patients assessed for adverse events to concomitant isotretinoin and laser therapy to date.

4.2 | Quality assessment

Recommendations on this important topic is limited by the lack of high-quality evidence of randomized controlled trials. Therefore, this systematic review does not include level 1 evidence. However, there are 5 level 2, 10 level 3, 3 level 4, and only one level 5 report. The majority of studies included are level 3 or higher. This review considers a greater body of evidence than that used to formulate current guidelines.

It is important to consider the limitation of all studies included in this review, including pre-intervention (eg, confounding, selection),

peri-intervention (eg, classification), and post-intervention (eg, reporting) bias. Eight studies^{7,8,18,19,21,22,29,31} were critically biased due to the inherent limitations of case reports and expert opinions of selective reporting and negative self-controls. The remainder were moderately biased, due to no pre-registered protocols, variable isotretinoin dosages and laser settings, and the subjective nature of outcome measures. Critically biased studies were the only to report keloid formation, whereas moderately biased studies reported transient adverse events, if any.

At a study level, limitations may include incomplete retrieval of all studies related to this topic or reporting bias. The inclusion of 12 databases and no language restrictions help counteract these forms of bias.

4.3 | Adverse events of isotretinoin alone

In considering any treatment regimen that includes more than one element, adverse events may be associated with both interventions together or due to one alone, crucial in the case of adverse events of concomitant isotretinoin and lasers. Spontaneous keloid transformation following isotretinoin therapy has been described in several case reports in which the patient has not been exposed to laser treatment, suggesting that these complications may be inherent to the medication rather than lasers.^{36,37} Therefore, it is possible that the presentation of keloids in two patients included in this systematic review may be due to isotretinoin alone.

4.4 | Recommendation

The summary of recommendations by treatment is described in Table 2. The majority of studies determine that laser intervention—whether for acne scar revision, hair removal, or otherwise—is associated with small or absent risk and produces a grade 1 recommendation due to consistent findings. Contraindication produces a grade 2B recommendation low-quality evidence of two case reports of one patient each.

Adverse events associated with different lasers and dosages of isotretinoin are described in Table 3. Ablative, nonablative, or a combination of laser therapies may be used during systemic isotretinoin treatment. There are no reliable differences between ablative and non-ablative laser therapy as keloid formation occurred in patients

TABLE 2 Summary of recommendations by laser intervention

Recommendation		Grade of Recommendation ³⁸	Level of Evidence ⁵
Safe	Acne or acne scar revision ^{11,14,15,17,18,20,23-30,32,34}	1	2, 3, and 5
	Laser hair removal ^{9-13,18,24,27}	1	2, 3, and 5
	Other (¹¹¹⁶¹⁹²¹²²³¹³³³⁵)	1	3, 4, and 5
Contraindicated	Acne scar revision	2B	4
	Laser hair removal		
	Other ⁽⁷⁸⁾		

TABLE 3 Adverse events sorted by laser subtype and isotretinoin dose

Ablative/ nonablative	Laser Type	Laser	Dosage	Adverse Events	References	
Ablative	Argon	Argon, 1.3 W,0.2 second	60 mg QD	Keloid formation in keloid-prone patient	7	
		CO ₂	10 600 nm CO ₂ fractional 38-42 mJ,5.51 J/cm ²	0.0005	Transient hyperpigmentation, self-resolving	29
	Erbium		1550 nm infrared fractional	10 mg QD	Transient mild acneiform eruption	15
			CO ₂ , 30 W, 1 ms	10-40 mg/d QD	Erythema/ crust, resolved 1 month.	25
			Ultrapulse CO ₂ , 800 W, 20-Hz, 0.3-msec	20 mg 6w		21
			CO ₂	150 mg/kg		22
			Ablative fractional CO ₂	Variable		20
			Ablative fractional	Varies		34
			1550 nm erbium-doped, 35-40 mJ, 8 passes	10 mg QD		23
			Er:YAG (19 J, 2 mm spot size, 3 Hz)	20 mg QD		31
	Fractionated erbium (50-70 mJ)	20 mg QD		17		
	Erbium doped 1550 nm NAFL	125-325 mg/kg		28		
Nonablative	Diode	810 nm diode	0.3-0.5 mg/kg QD	Spontaneously healing sparse crusting	10	
		810 nm diode, 80/90 W, 300 ms	20-80 mg QD	Transient bulla, resolved in 1 month	9	
	Erbium: glass fractional	1550 nm Erbium: glass fractional (20 mJ/cm ² , 100-169 points per area)	10 mg QD	Mild transient erythema	30	
			Variable		18	
	Multiple	Long-pulsed Nd-YAG laser and microfractional erbium glass	0.2-0.3 mg/kg/d		32	
			1064 nm Nd: YAG, 30-50 J/cm ² , 10-30 ms	0.5 mg/kg QD	Transient hyperpigmentation, resolved in 3 months	13
	Pulsed Dye	Pulsed dye	10 mg BID		19	
			595 nm Pulsed-dye (5-8 J/cm ²)	10 mg QD		33
			595 nm pulsed dye 7.5-8.5 J/cm ² , 1.5 ms	10 mg QD		35
	Pulsed	585 nm pulse dye,6.0 J/cm ²	Unknown	Keloid formation	8	
			1200 nm pulser, 22-27 J/cm ² ,20 ms	40-80 mg QD	None	12
	Multiple	Multiple	(a) CO ₂ ; (b) diode 980 nm hair removal	0.5 mg/kg QD + topical medication	(a) 8% patients transient hyperpigmentation, resolved 1-2 months; (b) none	24
(a) Nlite, 3 J/cm ² ; (b) ER: YAG, 0.6-0.7 J/cm ²			1 mg/kg QD	Hyperpigmentation at equal rate (3%) in both groups.	14	
(a) Long-pulsed Nd:YAG (1064 nm,9 mm,30 ms,40 J/cm ²) (b) Fractional ER:YAG 2940 nm, long pulse or scanner (c) Fractional CO ₂ 30 mj,pulse 0.04 second,100 pixel (d) Full face conventional CO ₂ resurfacing 3 mm spot,500 Hz (e) Q-switched Nd: YAG 1.5 mm spot,400mj			2-110 mg/kg	(a) None (b) resolving post- inflammatory pigmentation (c-d) None (e) transient erythema	27	
(a) Nonablative fractional (1540 nm, 100 mJ/mB, 3 passes); (b) ablative fractional laser (erbium:YAG 2940 nm, 91 J/cm ² , 3 passes); (c) full ablative (erbium:YAG 2940 nm, 2 J, 8 passes)			40 mg BID	(a) None; (b) None; (c) Mild erythematous scar	26	

TABLE 3 (Continued)

Ablative/ nonablative	Laser Type	Laser	Dosage	Adverse Events	References
		Quality-switched ruby, diode, intense pulsed, ER: YAG, Nlite, pulsed dye	Variable	None	11
		Erbium, vascular, Q-switched alexandrite, 532 nm Q-switched, 1064 nm Nd: YAG, and non-ablative fractional	Variable		16

under both modalities, and notably, these were case reports from prior to the turn of the century in possibly patients that were keloid-prone at baseline. In addition, isotretinoin dosage does not appear to impact the occurrence of adverse events as a patient on 60 mg qd developed a keloid, while no adverse events were noted in patients on even higher doses. Due to the two brief reports of adverse events occurring in patients prone to keloid formation, physicians should evaluate whether the patient is susceptible to pigmentation, scars, or keloid formation and consider a test treatment area prior to treatment as a standard.^{7,8} Patients should also be recommended to use a mild cleanser and moisturizer as well as sunscreen and sun avoidance post-treatment to decrease any possible associated risks.^{39,40}

The results of this systematic review are promising for patients and providers wishing to continue isotretinoin during laser treatment. We conclude that though there may be a risk associated with concomitant use of isotretinoin and lasers, the body of evidence indicates that this risk is relatively small or absent. Recent studies have demonstrated no difference in wound healing perioperatively between those individuals on systematic isotretinoin vs control.⁴¹ Further robust studies should be conducted to provide additional evidence that may challenge the current guidelines contraindication.

5 | CONCLUSION

The data presented fails to show long-term adverse effects of concomitant use of isotretinoin and lasers. It does not prove that isotretinoin use is safe at all dosages and with all lasers at all parameters. Further high-quality randomized controlled trials with a larger number of patients and treatments must be performed before it is concluded that concomitant use is completely safe in patients.

AUTHOR CONTRIBUTIONS

Mirza, Mirza had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Mirza, Mirza, Khatri. Acquisition, analysis, or interpretation of data: Mirza, Mirza. Drafting of manuscript: Mirza, Mirza. Critical revision of manuscript for important intellectual content: Khatri. Statistical Analysis: N/A. Obtained Funding: N/A. Administrative, technical, or material support: Mirza, Mirza, Khatri. Study supervision: Khatri.

ORCID

Fatima N. Mirza  <https://orcid.org/0000-0003-1299-6258>

REFERENCES

- Bickers DR, Lim HW, Margolis D, et al. The burden of skin diseases: 2004. *J Am Acad Dermatol*. 2006;55(3):490-500. <https://doi.org/10.1016/j.jaad.2006.05.048>.
- Fitzpatrick RE. Treatment of inflamed hypertrophic scars using intralesional 5-FU. *Dermatol Surg*. 1999;25(3):224-232. <http://www.ncbi.nlm.nih.gov/pubmed/10193972> Accessed May 20, 2017.
- Lupton JR, Alster TS. Laser scar revision. *Dermatol Clin*. 2002;20(1):55-65. [https://doi.org/10.1016/S0733-8635\(03\)00045-7](https://doi.org/10.1016/S0733-8635(03)00045-7).
- Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 2009;6(7):e1000097. <https://doi.org/10.1371/journal.pmed.1000097>.
- Howick, J. et al. (2011) The 2011 Oxford CEBM Levels of Evidence. <http://www.cebm.net/index.aspx?o=5653> Accessed January 31, 2017.
- Sterne JA, Harnán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ*. 2016;355:i4919. <http://www.ncbi.nlm.nih.gov/pubmed/27733354> Accessed February 2, 2017.
- Zachariae H. Delayed wound healing and keloid formation following argon laser treatment or dermabrasion during isotretinoin treatment. *Br J Dermatol*. 1988;118(5):703-706. <http://www.ncbi.nlm.nih.gov/pubmed/2969261> Accessed February 1, 2017.
- Bernstein LJ, Geronemus RG. Keloid formation with the 585-nm pulsed dye laser during isotretinoin treatment. *Arch Dermatol*. 1997;133(1):111-112. <http://www.ncbi.nlm.nih.gov/pubmed/9006390> Accessed February 1, 2017.
- Khatri KA. Diode laser hair removal in patients undergoing isotretinoin therapy. *Dermatol Surg*. 2004;30(9):1205-1207. <https://doi.org/10.1111/j.1524-4725.2004.30373.x>.
- Cassano N, Arpaia N, Vena GA. Diode laser hair removal and isotretinoin therapy. *Dermatol Surg*. 2005;31(3):380-381. <http://www.ncbi.nlm.nih.gov/pubmed/15841649> Accessed February 1, 2017.
- Moradi A et al. Co-administration of isotretinoin and laser treatments. *Lasers Surg Med*. 2005;36(17):39.
- Khatri K, Garcia V. Letter: light-assisted hair removal in patients undergoing isotretinoin therapy. *Dermatol Surg*. 2006;32(6):875-877. <https://doi.org/10.1111/j.1524-4725.2006.32182.x>.
- Khatri KA. The safety of long-pulsed Nd:YAG laser hair removal in skin types III-V patients during concomitant isotretinoin therapy. *J Cosmet Laser Ther*. 2009;11(1):56-60. <https://doi.org/10.1080/14764170802612984>.
- Moradi A et al. Co-administration of Nlite and Er:yag laser with isotretinoin. *Lasers Surg Med*. 2009;41:34-35.
- Hann S-K et al. Concomitant use of infrared fractional laser with low dose isotretinoin. *Lasers Surg Med*. 2010;25(22):22.

16. Alissa A. Concomitant use of laser and isotretinoin, how safe? *Lasers Surg Med.* 2011;43(23):943.
17. Leal H, Cantu P. Fractionated erbium laser during oral isotretinoin treatment. *J Am Acad Dermatol.* 2011;64(2, 1):AB18.
18. Patwardhan M et al. Isotretinoin and lasers: can they be used at the same time? *J Am Acad Dermatol.* 2012;66(4):AB28. <https://doi.org/10.1016/j.jaad.2011.11.123>.
19. Han J et al. A case of cutaneous Rosai-Dofman disease treated with isotretinoin and pulsed dye laser. *J Dermatol.* 2012;39(1):108.
20. Jeong M et al. Early ablative carbon dioxide fractional laser for acne scars in asian patients undergoing oral isotretinoin. *J Investig Dermatol.* 2013;133(1):S181.
21. Park HC, Kim EJ, Kim JE, Ro YS, Ko JY. Treatment of multiple eccrine hidrocystomas with isotretinoin followed by carbon dioxide laser. *J Dermatol.* 2013;40:414-415. <https://doi.org/10.1111/1346-8138.12059>.
22. Noh S, Shin JU, Jung JY, Lee JH. A case of sebaceous hyperplasia maintained on low-dose isotretinoin after carbon dioxide laser treatment. *Int J Dermatol.* 2014;53:e151-e153. <https://doi.org/10.1111/j.1365-4632.2012.05823.x>.
23. Yoon JH, Park EJ, Kwon IH, et al. Concomitant use of an infrared fractional laser with low-dose isotretinoin for the treatment of acne and acne scars. *J Dermatol Treat.* 2014;25(2):142-146. <https://doi.org/10.3109/09546634.2013.768758>.
24. Chandrashekar BS, Varsha DV, Vasanth V, Jagadish P, Madura C, Rajashekar ML. Safety of performing invasive acne scar treatment and laser hair removal in patients on oral isotretinoin: a retrospective study of 110 patients. *Int J Dermatol.* 2014;53(10):1281-1285. <https://doi.org/10.1111/ijd.12544>.
25. Kim HW, Chang SE, Kim JE, Ko JY, Ro YS. The safe delivery of fractional ablative carbon dioxide laser treatment for acne scars in Asian patients receiving Oral isotretinoin. *Dermatol Surg.* 2014;40(12):1361-1366. <https://doi.org/10.1097/DSS.000000000000185>.
26. Khatri KA, Iqbal N, Bhawan J. Laser skin resurfacing during isotretinoin therapy. *Dermatol Surg.* 2015;41(6):758-759. <https://doi.org/10.1097/DSS.000000000000353>.
27. Mahadevappa OH et al. Surgical outcome in patients taking concomitant or recent intake of oral isotretinoin: a multicentric study-ISO-AIMS study. *J Cutan Aesthet Surg.* 2016;9(2):106-112. <https://doi.org/10.4103/0974-2077.184054>.
28. Saluja SS et al. Safety of non-ablative fractional laser for acne scars within 1 month after treatment with oral isotretinoin: a randomized split-face controlled trial. *Lasers Surg Med.* 2017;49(10):886-890. <https://doi.org/10.1002/lsm.22711>.
29. Pestoni Porvén C, Vieira dos Santos V, del Pozo Losada J. Fractional carbon dioxide (CO₂) laser combined with topical tretinoin for the treatment of different forms of cystic acne. *J Cosmet Laser Ther.* 2017;19(8):465-468. <https://doi.org/10.1080/14764172.2017.1349323>.
30. Xia J, Hu G, Hu D, Geng S, Zeng W. Concomitant use of 1,550-nm nonablative fractional laser with low-dose isotretinoin for the treatment of acne vulgaris in asian patients: a randomized split-face controlled study. *Dermatol Surg.* 2018;44(9):1201-1208. <https://doi.org/10.1097/DSS.0000000000001546>.
31. Demirhan S. Treatment of multiple eccrine hidrocystoma with oral isotretinoin following erbium-yttrium aluminum garnet laser. *J Cosmet Laser Ther.* 2019;21(1):11-13. <https://doi.org/10.1080/14764172.2018.1427873>.
32. Gold M et al. Treatment of moderate to severe acne and scars with a 650-microsecond 1064-nm laser and isotretinoin. *J Drugs Dermatol.* 2020;19(6):19. <https://doi.org/10.36849/JDD.2020.5108>.
33. Kwon HH et al. Combined treatment of recalcitrant papulopustular rosacea involving pulsed dye laser and fractional microneedling radio-frequency with low-dose isotretinoin. *J Cosmet Dermatol.* 2020;19(1):105-111. <https://doi.org/10.1111/jocd.12982>.
34. Kim J et al. Safety of combined fractional microneedle radiofrequency and CO₂ as an early intervention for inflammatory acne and scarring treated with concomitant isotretinoin. *Dermatol Surg.* 2020;1. <https://doi.org/10.1097/dss.0000000000002364>. [Epub ahead of print].
35. Ma D, Li Q, Jin D, Sun M, Nie X. A case of lupus miliaris disseminatus faciei that was successfully treated with 595 nm pulsed-dye laser combined with drugs. *Dermatol Ther.* 2020;33:e13373. <https://doi.org/10.1111/dth.13373>.
36. Dogan G. Possible isotretinoin-induced keloids in a patient with Behcet's disease. *Clin Exp Dermatol.* 2006;31(4):535-537. <https://doi.org/10.1111/j.1365-2230.2006.02140.x>.
37. Ginarte M, Peteiro C, Toribio J. Keloid formation induced by isotretinoin therapy. *Int J Dermatol.* 1999;38(3):228-229. <http://www.ncbi.nlm.nih.gov/pubmed/10208624> Accessed January 31, 2017.
38. Robinson JK, Dellavalle RP, Bigby M, Callen JP. Systematic reviews. *Arch Dermatol.* 2008;144(1):97-99. <https://doi.org/10.1001/archdermatol.2007.28>.
39. Alexiades-Armenakas MR, Dover JS, Arndt KA. The spectrum of laser skin resurfacing: nonablative, fractional, and ablative laser resurfacing. *J Am Acad Dermatol.* 2008;58:719-737. <https://doi.org/10.1016/j.jaad.2008.01.003>.
40. Pozner JN, DiBernardo BE. Laser resurfacing: full field and fractional. *Clin Plast Surg.* 2016;43:515-525. <https://doi.org/10.1016/j.cps.2016.03.010>.
41. Tolkachjov SN, Sahoo A, Patel NG, Lohse CM, Murray JA, Tollefson MM. Surgical outcomes of patients on isotretinoin in the perioperative period: a single-center, retrospective analysis. *J Am Acad Dermatol.* 2017;77(1):159-161. <https://doi.org/10.1016/j.jaad.2017.03.019>.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Mirza FN, Mirza HN, Khatri KA. Concomitant use of isotretinoin and lasers with implications for future guidelines: An updated systematic review. *Dermatologic Therapy.* 2020;33:e14022. <https://doi.org/10.1111/dth.14022>