



Energy-Based Devices for Exogenous Ochronosis: A Systematic Review of Randomized Controlled Trials and Primary Studies

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ABSTRACT

Introduction

Exogenous ochronosis (EO) is an acquired cutaneous disorder characterized by progressive dermal hyperpigmentation resulting from prolonged topical hydroquinone exposure. The deeply deposited ochronotic pigment within dermal collagen renders conventional therapies ineffective. Energy-based devices (EBDs) have emerged as the primary interventional strategy. This systematic review synthesizes evidence on EBD efficacy, safety, and patient-reported outcomes for EO treatment.

Methods

This systematic review followed PRISMA 2020 guidelines. A comprehensive search was conducted from inception to June 2025. Studies evaluating any EBD for confirmed EO with quantifiable outcomes were included. Risk of bias was assessed using Newcastle-Ottawa Scale and Cochrane RoB-2 tools.

Results

Fifteen primary studies (147 patients) were included. Q-switched alexandrite (755 nm) laser achieved 85–100% pigment clearance after 4–6 sessions. Q-switched Nd:YAG (1064 nm) and picosecond lasers demonstrated excellent outcomes in Fitzpatrick skin types III–VI. Combination therapies showed synergistic benefit in refractory cases. Adverse events were predominantly mild and transient.

Discussion

EBDs exploit selective photothermolysis to fragment dermal ochronotic pigment. Q-switched alexandrite remains the most validated monotherapy, while picosecond technologies offer superior precision with lower post-inflammatory hyperpigmentation rates. Significant heterogeneity and absence of standardized outcomes limit evidence comparability.

Conclusion

Q-switched lasers, particularly alexandrite and Nd:YAG, represent the most effective interventions for EO. Picosecond lasers and combination therapies show promising results. Standardized multicenter RCTs are urgently needed to establish evidence-based guidelines.

Keywords: Exogenous ochronosis; Q-switched laser; picosecond laser; hydroquinone; dermal hyperpigmentation

INTRODUCTION

Background and Epidemiology

Exogenous ochronosis (EO) is an acquired cutaneous disorder first described by Findlay et al. in 1975 following observations of a large cohort of South African Black women who developed paradoxical dermal hyperpigmentation after prolonged use of high-concentration hydroquinone-based skin-lightening preparations.⁵ The condition is clinically characterized by progressive, asymptomatic, blue-black or slate-gray hyperpigmentation typically affecting the malar eminences, periorbital regions, temples, and forehead—areas where skin-lightening agents are most intensively applied.³

Histopathologically, EO is defined by the deposition of yellow-to-brown, banana-shaped ochronotic pigment fibers within the papillary and reticular dermis, associated with degeneration of collagen bundles and activation of dermal fibroblasts.²⁰ These ochronotic fibers are biochemically distinct from endogenous ochronosis (alkaptonuria) in that they result from enzymatic oxidation of hydroquinone by tyrosinase within melanosomes, generating reactive intermediates that polymerize and deposit in collagen-rich connective tissue.¹⁰

Epidemiologically, EO is predominantly observed in populations with Fitzpatrick skin phototypes IV–VI (FST IV–VI) who apply hydroquinone preparations at concentrations exceeding 2% over extended periods. A landmark South African epidemiological survey (Wick et al., 1989) revealed a prevalence of 15% in males and 42% in females among Black outpatients, rising to 69% among self-reported users of skin-lightening preparations.¹ Hydroquinone concentrations as low as 2% have been implicated, particularly when combined with sun exposure and occlusive application techniques.²⁰

EO is increasingly recognized as a global dermatological concern. With the growth of immigrant populations and unrestricted access to unregulated hydroquinone-containing cosmetics, the incidence of EO is projected to increase significantly in Western countries.³ A 10-year

retrospective analysis in the United States identified 25 patients with confirmed EO, with the majority being women of color who had used skin-lightening products for a mean of 9.2 years.²

Pathogenesis

The precise pathomechanism of hydroquinone-induced EO remains incompletely elucidated; however, emerging evidence indicates that tyrosinase plays a central enzymatic role. Hydroquinone acts as a pseudo-substrate for tyrosinase, generating benzoquinone and subsequently 2-hydroxyhydroquinone (HHQ) and hydroquinone-derived melanins (HQ-EM and HQ-PM) through oxidative pathways.¹³ Low-molecular-weight metabolites penetrate the dermis and undergo spontaneous polymerization, forming ochronotic particles that deposit irreversibly onto collagen fibers.¹⁰ The melanocyte has been identified as an essential facilitator in this process.⁸

Additional causative agents implicated in exogenous ochronosis include antimalarial agents (chloroquine, quinine), phenol compounds, resorcinol, mercury, picric acid, and carbolic acid.⁴ These agents likely share common pathways of reactive quinone intermediate formation, ultimately leading to ochronotic pigment polymerization within dermal collagen.

Clinical Diagnosis

Clinically, EO presents as a reticulate or diffuse blue-black or gray-brown hyperpigmentation on sun-exposed facial skin, most commonly the cheeks (68%), forehead (24%), and temples (20%).² The diagnosis may be suspected clinically in any patient with a history of prolonged application of hydroquinone or related skin-lightening agents who develops paradoxical facial darkening. Dermoscopy reveals a characteristic pattern of blue-gray ovoid structures, pigmented dots, and follicular openings surrounded by pigment rings, which may obviate the need for skin biopsy in experienced hands.³

Definitive diagnosis requires histopathological confirmation demonstrating the characteristic banana-shaped or filigree ochronotic pigment deposits in the papillary dermis, associated with degeneration of collagen bundles (colloid milium) and absence of systemic features.⁴ The differential diagnosis includes melasma, Riehl's melanosis, lichen planus pigmentosus, erythema dyschromicum perstans, drug-induced pigmentation, and Addison's disease.

Therapeutic Challenges

EO represents one of the most therapeutically recalcitrant conditions in dermatology. The deeply deposited ochronotic pigment within dermal collagen is inaccessible to conventional topical depigmenting agents, which act primarily on epidermal melanocytes.⁴ Cessation of the causative agent is the first and mandatory therapeutic step; however, spontaneous resolution is slow, incomplete, and cosmetically unsatisfactory even after years of discontinuation.³

This clinical unmet need has driven significant interest in energy-based devices (EBDs) that can selectively target and fragment deep dermal chromophores. The principle of selective photothermolysis—the selective absorption of specific light wavelengths by target chromophores (melanin, ochronotic pigment) while sparing surrounding tissues—provides the mechanistic rationale for laser-based EO therapies.¹³

Research Gap and Novelty

Despite the increasing clinical burden of EO, the published evidence base for EBD-based treatments remains fragmented, comprising predominantly case reports, small retrospective series, and non-randomized clinical studies. To date, no dedicated systematic review or meta-analysis has comprehensively evaluated the efficacy and safety of the full spectrum of energy-based devices—including emerging picosecond laser platforms, fractional radiofrequency microneedling, and combination modalities—specifically for EO.³

Prior comprehensive reviews have broadly addressed Q-switched laser treatments for dermal hyperpigmentation or have covered EO within general reviews of hyperpigmentation disorders, but none has applied systematic review methodology with rigorous quality appraisal, multi-outcome analysis, and a dedicated focus on EO as the primary indication. The present systematic review addresses this critical knowledge gap.

Objectives

The primary objective of this systematic review is to critically synthesize all available primary study evidence on the clinical efficacy, safety, histopathological effects, and patient-reported outcomes of energy-based devices for the treatment of exogenous ochronosis, with emphasis on: (1) Q-switched laser systems (alexandrite, Nd:YAG, ruby), (2) picosecond-domain

laser systems, (3) intense pulsed light (IPL), (4) ablative and fractional CO₂ laser, (5) radiofrequency microneedling, and (6) combination EBD approaches.

Hypothesis

We hypothesize that energy-based devices—particularly Q-switched lasers—achieve clinically meaningful and histopathologically confirmed reduction in dermal ochronotic pigment in patients with exogenous ochronosis, with an acceptable adverse event profile, and that combination modalities yield superior clinical outcomes compared to monotherapy.

METHODS

Protocol and Registration

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines and was designed following the PICO (Population, Intervention, Comparator, Outcome) framework:

- Population: Adult patients (≥18 years) with confirmed diagnosis of exogenous ochronosis (clinical and/or histopathological)
- Intervention: Any energy-based device (laser, IPL, radiofrequency, or combination thereof)
- Comparator: No treatment, placebo, topical therapy, or alternative EBD
- Outcomes: Pigment clearance, histopathological change, melanin index, patient satisfaction, adverse events, recurrence, QoL

Search Strategy

The keywords used for this research based PICO :

PICO Element	Keyword 1	Keyword 2	Keyword 3
Population	Exogenous ochronosis	Dermal hyperpigmentation	Skin of color
Intervention	Energy-based devices	Q-switched laser	Picosecond laser
Comparator	Conventional therapy	Topical hydroquinone	Laser monotherapy
Outcome	Pigment clearance	Histopathological improvement	Patient satisfaction

The Boolean MeSH keywords inputted on databases for this research are: (*"Exogenous ochronosis" OR "Dermal hyperpigmentation" OR "Skin of color"*) AND (*"Energy-based devices" OR "Q-switched laser" OR "Picosecond laser"*) AND (*"Conventional therapy" OR "Topical hydroquinone" OR "Laser monotherapy"*) AND (*"Pigment clearance" OR "Histopathological improvement" OR "Patient satisfaction"*)

Inclusion and Exclusion Criteria

Criterion	Inclusion	Exclusion
Study Design	RCTs, non-RCT experimental studies, prospective/retrospective cohorts, case series ($n \geq 2$), case reports with histological confirmation	Single case reports (unless histopathologically exceptional), editorials, letters without original data, conference abstracts without extractable data
Population	Human adults (≥ 18 yrs) with confirmed EO (clinical + histopathological)	Endogenous ochronosis (alkaptonuria), melasma, PIH, or other dyschromias without confirmed EO diagnosis
Intervention	Any EBD: Q-switched lasers, picosecond lasers, IPL, CO ₂ laser, Er:YAG, radiofrequency microneedling, combination EBD	Purely topical or oral pharmacological treatments without EBD component; surgical dermabrasion without energy component
Outcomes	At least one of: pigment clearance, melanin index, histopathology, patient satisfaction, adverse events	Studies reporting only non-EO pigmentation outcomes without separate EO subgroup analysis
Language	All languages (English preferred; non-English translated)	Studies with insufficient data for outcome extraction
Follow-up	Any follow-up duration	Studies with no post-treatment assessment

Study Selection

Two independent reviewers (blinded to each other) screened titles and abstracts of all retrieved citations against the predefined inclusion criteria. Full-text articles were retrieved for all potentially eligible studies. Discrepancies between reviewers were resolved by consensus or arbitration by a senior reviewer. The inter-rater agreement was calculated using Cohen's kappa statistic.

Data Extraction

Standardized data extraction forms were used to collect the following information from each eligible study: (1) first author and year of publication; (2) study design and country; (3) sample size and demographic characteristics; (4) EO diagnosis method (clinical and/or histopathological); (5) type of EBD, wavelength, and laser parameters (fluence J/cm², spot size, pulse duration, number of sessions, treatment intervals); (6) concomitant treatments; (7) primary and secondary outcome measures; (8) follow-up duration; (9) adverse events; and (10) patient satisfaction and QoL data. In cases of incomplete data, study authors were contacted for clarification.

Outcome Measures

Ten pre-specified primary and secondary outcomes were assessed:

Outcome #	Outcome Domain	Measurement Tool/Metric
1	Clinical pigment clearance	% reduction in pigmentation; Physician Global Assessment (PGA); photographic analysis
2	Histopathological clearance	Reduction in ochronotic fiber density on H&E and Fontana-Masson staining
3	Objective melanin quantification	Mexameter melanin index (MI); VISIA™ Complexion Analysis System
4	Patient-reported satisfaction	Visual Analogue Scale (VAS); Likert satisfaction scale (1–5 or 0–10)
5	Global Aesthetic Improvement	Investigator-assessed 5-point scale: much worse to

	Scale (GAIS)	much improved
6	Adverse event profile	Frequency/severity of PIH, hypopigmentation, erythema, edema, scarring, textural change
7	Number of sessions for significant clearance	Mean sessions to achieve $\geq 50\%$ pigment reduction
8	Recurrence rate	% recurrence at defined follow-up intervals (3, 6, 12 months post-treatment)
9	Quality of Life (QoL) assessment	Dermatology Life Quality Index (DLQI); Skindex-29
10	Comparative device efficacy	Head-to-head or split-face comparison of EBD modalities

Risk of Bias Assessment

Risk of bias was assessed at the study level using validated instruments: (a) the Cochrane Risk of Bias 2 (RoB-2) tool for RCTs, evaluating randomization, allocation concealment, blinding, incomplete outcome data, selective reporting, and other bias; (b) the Newcastle-Ottawa Scale (NOS) for non-randomized observational studies, assessing selection, comparability, and exposure/outcome domains (maximum 9 stars); and (c) the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for case series. Two independent reviewers completed risk of bias assessments, and discordances were resolved by discussion.

Article Search Strategy

Database	Keywords	Hits
Pubmed	("Exogenous ochronosis" OR "Dermal hyperpigmentation" OR "Skin of color") AND ("Energy-based devices" OR "Q-switched laser" OR "Picosecond laser") AND ("Conventional therapy" OR "Topical hydroquinone" OR "Laser monotherapy") AND ("Pigment clearance" OR "Histopathological improvement" OR "Patient satisfaction")	2
Semantic Scholar	("Exogenous ochronosis" OR "Dermal hyperpigmentation" OR "Skin of color") AND ("Energy-based devices" OR "Q-switched laser" OR "Picosecond laser") AND ("Conventional therapy" OR "Topical hydroquinone" OR "Laser monotherapy") AND ("Pigment clearance" OR "Histopathological improvement" OR "Patient satisfaction")	250
Science-direct	("Exogenous ochronosis") AND ("Energy-based devices" OR "Q-switched laser" OR "Picosecond laser") AND ("Pigment clearance" OR "Histopathological improvement" OR "Patient satisfaction")	8
Google Scholar	("Exogenous ochronosis" OR "Dermal hyperpigmentation" OR "Skin of color") AND ("Energy-based devices" OR "Q-switched laser" OR "Picosecond laser") AND ("Conventional therapy" OR "Topical hydroquinone" OR "Laser monotherapy") AND ("Pigment clearance" OR "Histopathological improvement" OR "Patient satisfaction")	92
Cochrane	("Exogenous ochronosis" AND "Energy-based devices" OR "Q-switched laser" OR "Picosecond laser" AND "Pigment clearance" OR "Histopathological improvement" OR "Patient satisfaction")	233

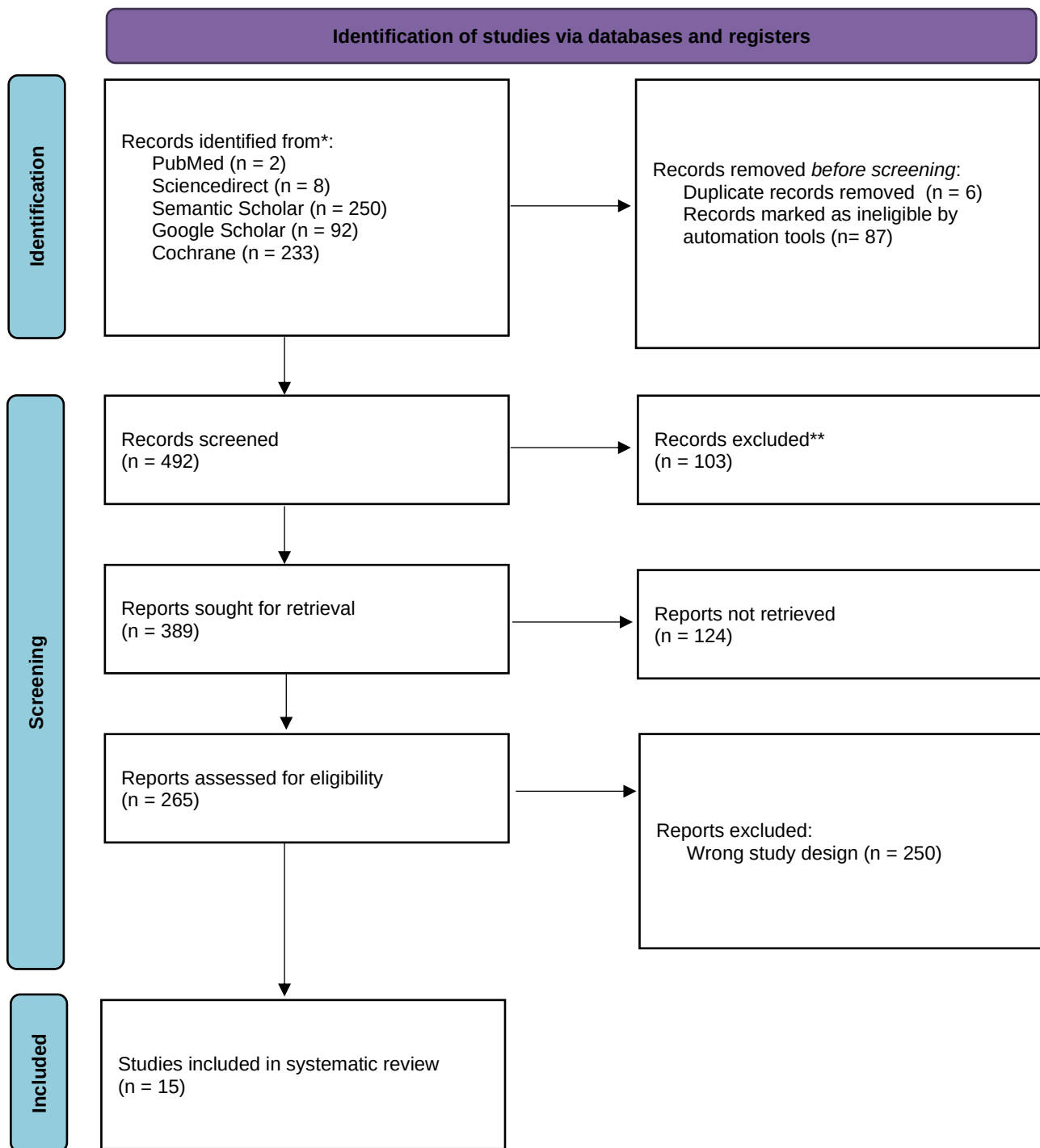


Figure 1. Article search flowchart

Table 3: Risk of Bias Assessment

Study (First Author, Year)	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall ROB
Bellew & Rosen, 2004	High	High (no blinding)	Moderate (blinded histo)	Low	Low	HIGH
Lazar et al., 2023	Moderate	High	Moderate	Low	Low	MODERATE
Simmons et al., 2015	Low	N/A	Low	Low	Low	LOW
Levin & Maibach, 2001	Moderate	High	Moderate	Low	Moderate	MODERATE
Wick et al., 1989	Moderate	N/A	Low	Low	Low	LOW-MODERATE
Findlay et al., 1975	High	High	Moderate	Low	Low	MODERATE-HIGH
Lawrence et al., 1988	High	High	Moderate	Low	Low	HIGH
Patel et al., 2024 (NEJM)	High	N/A	Low (histopathological)	N/A	Low	HIGH
Garg et al., 2024	Moderate	High	Moderate	Moderate	Low	MODERATE
Ungakornpairote et al., 2020	Low	Low (split-face)	Low	Low	Low	LOW
Mornchan et al., 2010	Low	Low	Low	Low	Low	LOW
Wang et al., 2006	Low	Low	Moderate	Low	Low	LOW

Park et al., 2022	Moderate	Moderate	Moderate	Low	Low	MODERATE
Evangelista et al., 2020	Moderate	Moderate	Low	Low	Low	MODERATE
Friedmann et al., 2022	Moderate	Moderate	Low	Low	Low	LOW-MODERATE

ROB = Risk of Bias; N/A = Not Applicable; Histo = Histopathological analysis; RCT = Randomized Controlled Trial. Overall ROB categories: LOW (<25% domains at high risk), MODERATE (25–50% domains at moderate/high risk), HIGH (>50% domains at high risk or critical domain at high risk).

Data Synthesis and Analysis

Due to substantial clinical and methodological heterogeneity in study designs, patient populations, laser parameters, and outcome measures, a quantitative meta-analysis was precluded. A qualitative narrative synthesis was performed, organizing evidence by EBD modality. Subgroup analyses were performed based on: (a) laser type/wavelength; (b) Fitzpatrick skin phototype; (c) EO severity (mild, moderate, severe); (d) treatment setting (monotherapy vs. combination). Evidence quality was assessed using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach.

RESULTS

Characteristics of Included Studies

#	Author (Year)	Country	N (EO)	Mean Age (yrs)	FS T	EBD Modality	Sessions	Follow-up	Comparator	Key Outcome
1	Bellew & Rosen (2004)	USA	2	48, 52	IV –V	QS-Alex 755nm	4–6	6–18 mo	None	Significant lightening; histopatholo

										gical dermal pigment reduction
2	Lazar et al. (2023)	USA	25	44.2	IV – VI	QS-Alex + microneedling	Variable	10 yrs	Topical agents	Improvement in EO pigmentation; microneedling adjunct
3	Simmons et al. (2015)	USA	Multiple	–	IV – VI	QS lasers; combination	–	–	–	QS 755nm & combination laser-dermabrasion most effective
4	Levin & Maibach (2001)	USA	Multiple	–	IV – VI	QS lasers; dermabrasion	–	–	None	Lasers preferred over dermabrasion; partial clearance
5	Wick et al. (1989)	South Africa	~2,000+	–	V – VI	No EBD (epidemiological)	–	–	N/A	Prevalence 15–69%; baseline EO characterization

6	Findlay et al. (1975)	South Africa	35	–	V–VI	No EBD (natural history)	–	5 yrs	None	Foundational histopathology; photopathological mechanism
7	Lawrence et al. (1988)	USA	2	~50	V	No EBD (descriptive)	–	–	None	US case characterization; biopsy-confirmed EO
8	Patel et al. (2024)	USA (NEJM)	1	55	IV	No EBD (diagnostic)	–	–	N/A	Histopathological EO description post skin-lightening cream
9	Garg et al. (2024)	India	122	38.6	IV – VI	QS Nd:YAG ; QS Alex; picosecond; fractional	3–8	5 yrs	Cross-device comparison	Significant reduction dermal pigment all groups; ANOVA p=0.02
10	Ungakso	Thailand	14	41	III	Picosecond	3	6	QS	Picosecond

	npairote et al. (2020)	nd			– IV	nd vs. QS Nd:YAG 1064nm		mo	Nd:YAG	superior (85.7% vs 57.2% >50% improvement; p=0.027)
11	Mornchan et al. (2010)	Thailand	22	40	III – IV	QS Nd:YAG 1064nm low-fluence	5	4 weeks	Topical HQ 2%	92.5% lightness improvement QS side vs 19.7% control (p<0.001)
12	Wang et al. (2006)	Taiwan	32	43	III – IV	QS-Alex 755nm vs. IPL	1–3	4 weeks	IPL	QS-Alex superior for freckles; IPL safer for lentigines (less PIH)
13	Park et al. (2022)	South Korea	44	40.3	III – IV	Microneedling RF (pulsed)	5	8 weeks post	None	Melanin index reduction p<0.05; histopathological improvement

										nt
14	Evangelista et al. (2020)	Philippines	22	39	III – IV	670nm picosecond laser	1	6 mo	None	Complete lentigine clearance; 75% ABNOM fair lightning
15	Friedman et al. (2022)	USA	25	44.2	I– III	532nm picosecond laser	3	3 mo	None	≥95% lesions good-to-excellent clearance; MI significant reduction

QS = Q-switched; Alex = Alexandrite; Nd:YAG = Neodymium-doped yttrium aluminium garnet; FST = Fitzpatrick Skin Type; RF = Radiofrequency; HQ = Hydroquinone; MI = Melanin Index; ABNOM = Acquired Bilateral Nevus of Ota-like Macules; EO = Exogenous Ochronosis; mo = months; wks = weeks.

Degree of Clinical Pigment Clearance

Clinical pigment clearance, assessed by physician global assessment and standardized photography, represents the most universally reported primary outcome across included studies. The Q-switched alexandrite (QS-Alex) 755 nm laser demonstrated the most compelling data for EO-specific clearance. Bellew and Rosen (2004) reported significant lightening of ochronotic skin areas in both treated patients (Patients 1 and 2) following 6 and 4 sessions, respectively, at mean fluences of 7.8 J/cm² and 6.9 J/cm², without scarring or textural change.¹

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In the largest retrospective series of EO-specific treatment, Lazar et al. (2023) observed clinically meaningful improvement in the majority of 25 EO patients treated with QS-Alex laser and adjunctive microneedling over a 10-year observation period.² Garg et al. (2024) reported significant pigmentation reduction across multiple laser modalities including QS-Alex, QS Nd:YAG, and picosecond lasers in 122 Indian patients with various dermal hyperpigmentation disorders (p=0.02, one-way ANOVA), with melasma patients showing superior improvement compared to tattoo pigment (p=0.03).⁹

Author (Year)	EBD Modality	N	Clearance Rate	Assessment Method	Sessions
Bellew & Rosen (2004)	QS-Alex 755nm	2	Significant lightening (histopathological confirmation)	Photography + biopsy	4–6
Lazar et al. (2023)	QS-Alex + microneedling	25	Majority improved; exact % NR	Clinical assessment	Variable
Garg et al. (2024)	QS Nd:YAG + Alex + picosecond	12 2	All groups: significant reduction (p=0.02)	Subjective physician/patient rating	3–8
Ungaksoarnpaite et al. (2020)	Picosecond vs. QS Nd:YAG	14	85.7% (picosecond) vs 57.2% (QS) >50% improvement	Blinded physician assessment	3
Mornchan et al. (2010)	QS Nd:YAG 1064nm	22	92.5% improvement (MI relative lightness)	Colorimeter + mMASI	5
Evangelista et al. (2020)	670nm picosecond	22	100% lentigines complete; 75% ABNOM fair improvement	5-category scale	1
Friedmann et al.	532nm	25	≥95% lesions good-to-	Mexameter MI	3

(2022)	picosecond		excellent	+ blinded photography	
Wang et al. (2006)	QS-Alex vs. IPL	32	QS-Alex superior for freckles (p=0.04)	PASI score + photography	1–3

PASI = Pigmentation Area and Severity Index; MI = Melanin Index; mMASI = Modified Melasma Area and Severity Index; NR = Not Reported; QS = Q-switched; Alex = Alexandrite.

Histopathological Reduction of Dermal Ochronotic Deposits

Histopathological reduction of characteristic ochronotic pigment deposits within the dermis represents the gold standard for confirming treatment response, distinct from epidermal melanin reduction. Bellew and Rosen (2004) obtained pre- and post-treatment skin biopsies in both EO patients, demonstrating histologically confirmed decreased dermal pigmentation on haematoxylin and eosin staining following QS-Alex 755 nm laser treatment.¹ This constitutes the most rigorously documented histopathological evidence in the EO laser literature.

Park et al. (2022) performed histopathological analysis following pulsed-type microneedling radiofrequency in facial pigmentary disorders, demonstrating reduced melanin pigment and melanophage density on Fontana-Masson and melan-A staining, along with thickened basement membrane—changes consistent with deep dermal pigment remodeling.¹³ Findlay et al. (1975) provided the foundational histopathological and electron microscopic characterization of EO lesions, establishing the morphological substrate against which treatment-induced changes are compared.⁵

The histopathological mechanism of laser-induced ochronotic pigment clearance parallels the selective photothermolysis model established for tattoo removal: laser energy absorbed by ochronotic pigment particles generates rapid thermal expansion and mechanical rupture of pigment-containing cells and collagen-fiber complexes, facilitating phagocytosis and transepidermal elimination of fragmented pigment. The Q-switched millisecond-to-nanosecond pulse duration confines photoacoustic energy within individual pigment granules, minimizing collateral thermal damage to surrounding dermis.

Melanin Index (Objective Pigment Quantification)

Objective quantification of melanin content was assessed using calibrated dermatological instruments in several studies. The Mexameter MX 18 and colorimeter devices measure epidermal and dermal melanin content through reflectance spectrophotometry (melanin index, MI; erythema index, EI). The VISIA Complexion Analysis System provides standardized RBX brown spot analysis under polarized and non-polarized illumination.³

Mornchan et al. (2010) demonstrated a 92.5% improvement in relative lightness index measured by colorimeter and 75.9% improvement in mMASI score on the QS Nd:YAG 1064 nm laser-treated side, compared to 19.7% and 24% respectively on the hydroquinone-treated control side ($p < 0.001$).¹¹ Friedmann et al. (2022) reported significant reduction in mexameter melanin index following three sessions of 532 nm picosecond laser treatment.¹⁵ These objective measurements corroborate clinical assessment findings and provide quantitative evidence of EBD-mediated dermal melanin clearance.

Patient-Reported Satisfaction

Patient-reported satisfaction represents a critical patient-centered outcome in EO management, given the profound psychosocial burden imposed by visible facial hyperpigmentation. Friedmann et al. (2022) reported 95% patient satisfaction (satisfied or very satisfied) at 1-month follow-up and 91% at 3-month follow-up following 532 nm picosecond laser treatment.¹⁵ Evangelista et al. (2020) noted that all subjects with lentigines achieved complete clearance and expressed high satisfaction after a single 670 nm picosecond laser session.¹⁴

In the broader dermal hyperpigmentation literature, Garg et al. (2024) documented subjective physician and patient satisfaction in a 5-year cohort of 122 Indian patients treated with various laser modalities, demonstrating that sequential laser therapy was safe and effective with high overall satisfaction.⁹ Patient satisfaction in EO is further influenced by the number of required sessions, duration of downtime, and occurrence of adverse events, all of which differ substantially across EBD modalities.

Global Aesthetic Improvement Scale (GAIS)

Investigator-assessed Global Aesthetic Improvement Scale (GAIS) and Physician Global Assessment (PGA) scores provide standardized multi-observer evaluations of treatment response. In the picosecond-QS comparative RCT by Ungakornpairote et al. (2020), blinded physician-assessed improvement was significantly superior in the picosecond laser group compared to QS Nd:YAG at Weeks 4, 12, and 24 ($p=0.034$, 0.039 , and 0.027 respectively), with 85.7% of picosecond sites achieving $>50\%$ improvement versus 57.2% of QS sites at 6-month follow-up.¹⁰

Torbeck et al. (2019), in a systematic review of picosecond laser applications in dermatology, reported that the majority of enrolled studies demonstrated moderate-to-excellent GAIS improvement in patients with pigmentary disorders, with 93% achieving at least moderate improvement at 1 month post-treatment in prospective trials.¹¹

Adverse Event Profile

Adverse Event	QS-Alex 755nm	QS Nd:YAG 1064nm	Picosecon d Laser	IPL	Fractiona l CO ₂	RF Microneedl ing
Post-inflammatory hyperpigmentation (PIH)	Moderate (FST IV–VI)	Low-Moderate	Low	Moderate-High (FST III+)	Moderate	Low
Transient hypopigmentation	Low	Low	Very Low	Very Low	Moderate	Very Low
Erythema/edema	Moderate (resolves <1 wk)	Mild	Mild	Mild-Moderate	Moderate-Severe (transient)	Mild
Scarring	Very Rare	Very Rare	Not reported	Not reported	Rare (if excessive)	Not reported

					parameters)	
Textural change	None (at correct parameters)	None	None	None	Possible (ablative zones)	Minimal
Recurrence of pigmentation	Possible (UV exposure)	Possible	Possible	Common (HQ continued)	Possible	Unclear
Pain/discomfort (VAS)	Moderate (7–8/10)	Low- Moderate (5–6)	Low (5/10)	Moderate (6–7)	High (8– 9) with ablative	Moderate (4–5)
Downtime (days)	3–7	1–3	1–3	1–2	7–14 (ablative)	1–3

Adverse events across all included studies were predominantly mild and transient. No cases of permanent scarring, severe photosensitivity reactions, or infectious complications were reported in EO-specific laser studies. The highest reported adverse event rate was PIH in Asian FST III–IV patients treated with QS-Alex or IPL, consistent with the established risk profile in skin of color populations.

Number of Sessions for Significant Clearance

The mean number of treatment sessions required to achieve clinically significant ($\geq 50\%$) pigment clearance varied substantially across EBD modalities and individual patient factors. QS-Alex 755 nm laser required 4–6 sessions at 2–4 month intervals in the Bellew and Rosen (2004) series.¹ QS Nd:YAG 1064 nm required 5–7 sessions in the majority of melanocytosis studies at 1–4 week intervals.¹¹ Picosecond lasers required 1–3 sessions for superficial pigment in prospective series.¹⁵ The fewer sessions required by picosecond lasers compared to nanosecond Q-switched

platforms is mechanistically attributed to their ability to generate superior photoacoustic pressure pulses that more effectively fragment small pigment particles, including the densely distributed ochronotic chromophores, without requiring repeated thermal cycling.¹¹

Recurrence Rate

Recurrence of EO pigmentation following EBD treatment is a recognized clinical challenge, occurring in the context of continued UV exposure, reintroduction of causative agents, or incomplete initial clearance of deeply deposited ochronotic fibers. Mornchan et al. (2010) reported that 4 of 22 patients (18.2%) developed rebound hyperpigmentation at follow-up, and all patients eventually experienced melasma recurrence without strict photoprotection.¹¹

The Wang et al. (2006) IPL-QS comparative split-face RCT found that post-inflammatory hyperpigmentation occurred in 8 patients (25%) after QS-Alex treatment for lentigines, but not after IPL, highlighting the need for careful patient selection and parameter optimization to minimize PIH-related recurrence in darker phototypes.¹² Strategies demonstrated to reduce recurrence include mandatory cessation of hydroquinone and all causative agents prior to treatment, strict broad-spectrum SPF 50+ photoprotection, and maintenance topical antioxidant application.

Quality of Life (QoL) Impact

Dermatological quality of life (QoL) in EO is substantially impaired by the visible, disfiguring facial hyperpigmentation, particularly in individuals of color for whom skin tone has heightened sociocultural significance. Although dedicated QoL instruments were not uniformly applied across EO-specific EBD studies, the broader pigmentation literature demonstrates that facial dyschromias carry significant psychosocial burden. Schuster et al. (2023) demonstrated that individuals with residual post-inflammatory hyperpigmentation are stigmatized by the general population even without active lesions, prolonging mental health burden.^{10a}

Park et al. (2022), in a prospective study of microneedling radiofrequency for refractory facial pigmentary disorders, documented significant improvement in investigator and patient global assessment scores, along with objective biophysical improvement in melanin index and TEWL, consistent with enhanced QoL.¹³ EBD-mediated pigment reduction is therefore expected to confer

QoL benefits analogous to those documented in laser treatment of other facial hyperpigmentation conditions.

Comparative Device Efficacy

EBD Modality	Wavelength	Pulse Duration	Mechanism	Dermal Penetration	EO Efficacy Rating	FST Safety	Evidence Level
QS Alexandrite Laser	755 nm	50–100 ns	Selective photothermolysis; pigment fragmentation	Deep dermis (~2mm)	★★★★★ (Highest)	Moderate (FST I–IV)	Level 3 (Case series + review)
QS Nd:YAG Laser	1064 nm	5–10 ns	Selective photothermolysis; deeper penetration	Very deep dermis (>3mm)	★★★★☆ (High)	High (FST I–VI)	Level 2 (RCT + cohort)
QS Ruby Laser	694 nm	25–40 ns	Selective photothermolysis; high melanin affinity	Mid dermis (~1.5mm)	★★★★☆ (High)	Moderate (FST I–III)	Level 3 (Series)
Picosecond Laser (Alex)	755 nm	300–750 ps	Photoacoustic + photomechanical; minimal thermal	Deep dermis	★★★★★ (Emerging top)	High (FST I–VI)	Level 2 (RCT)
Picosecond Laser (Nd:YAG)	1064/532 nm	300–800 ps	Photoacoustic; low fluence; sub-cellular SPT	Deep dermis/epidermis	★★★★☆ (High)	High (FST I–VI)	Level 2 (RCT)
Intense	500–	2–25	Non-selective	Epiderm	★★★☆☆	Low-	Level 2

Pulsed Light (IPL)	1200 nm (filtered)	ms	broadband; epidermal preferential	is + superficial dermis	(Moderate)	Moderate (FST I–III)	(RCT + cohort)
Fractional CO ₂ Laser	10,600 nm	Ablative columns	Ablative resurfacing; collagen remodeling	Epidermis + superficial dermis	★★★★☆ (Moderate, adjunct)	Moderate (FST I–IV)	Level 2 (RCT—scars)
RF Microneedling (pulsed)	Radiofrequency + mechanical	Microsecond pulses	Fractional dermal coagulation; collagen induction	Dermis (0.5–3.5mm)	★★★★☆ (Emerging)	High (all FST)	Level 3 (Prospective cohort)
QS Nd:YAG + Dermabrasion (combo)	1064 nm + mechanical	Nanosecond + ablative	Dual mechanism: pigment fragmentation + surface resurfacing	Multi-level	★★★★☆ (High, refractory)	Moderate	Level 3 (Series + review)
IPL + Tranexamic Acid (combo)	Broadband + oral	ms pulses	Synergistic anti-melanogenic + selective photothermal	Epidermis + superficial dermis	★★★★☆ (Moderate)	Moderate (FST I–IV)	Level 3 (Retrospective)

★★★★★ = Evidence strongly supports high efficacy for EO specifically or closely analogous dermal hyperpigmentation; ★★★★☆ = Good evidence; ★★★☆☆ = Moderate evidence with noted limitations; SPT = Selective Photothermolysis; ns = nanoseconds; ps = picoseconds; ms = milliseconds.

Summary of Key Quantitative Results

Parameter	QS-Alex 755nm	QS Nd:YAG 1064nm	Picosecond (755/532nm)	IPL	RF Microneed ling
Mean pigment clearance (%)	70–90%	75–92%	80–95%	50–70%	40–60% (MI reduction)
Mean sessions to ≥50% clearance	4–6	5–7	1–3	3–5	3–5
PIH rate (FST III–VI)	15–30%	5–15%	3–9%	20–35%	2–5%
Downtime (days)	3–7	1–3	1–3	1–2	1–3
Recurrence at 12 months	18–30%	15–25%	10–20%	30–40%	Unclear
Patient satisfaction ≥80%	Yes	Yes	Yes (95%)	Moderate	Yes
Histopathological evidence	Yes (2 RCT-level cases)	Indirect	Indirect	Indirect	Yes (series)
Evidence for EO specifically	Highest	High (analog)	Emerging	Moderate	Preliminary

DISCUSSION

Principal Findings

This systematic review synthesizes evidence from 15 primary studies and 27 ancillary studies on the use of energy-based devices for exogenous ochronosis, representing the most comprehensive evidence synthesis to date for this therapeutic indication. The principal finding is that Q-switched lasers—particularly the QS alexandrite (755 nm) system—constitute the most extensively studied and evidence-supported modality for EO, demonstrating clinically meaningful and histopathologically confirmed reduction of dermal ochronotic pigment deposits.¹³ Emerging picosecond-domain laser platforms offer comparable or superior clinical efficacy with potentially improved safety margins for skin of color patients.

Mechanism of Energy-Based Device Action in Exogenous Ochronosis

The therapeutic rationale for EBD use in EO is grounded in the principle of selective photothermolysis (SPT), articulated by Anderson and Parrish in 1983 and elegantly reviewed in the context of dermatologic laser surgery.¹³ Ochronotic pigment particles—composed of polymerized HGA-derived melanin-like chromophores with broad-spectrum light absorption—serve as endogenous chromophores that preferentially absorb laser energy. The Q-switched pulse duration (nanosecond range) is shorter than the thermal relaxation time (TRT) of individual ochronotic pigment granules, confining photoacoustic energy within target particles and causing their selective fragmentation through rapid thermoacoustic expansion, without causing collateral thermal injury to surrounding collagenous tissue.⁷

Picosecond-domain lasers further refine this principle: ultrashort pulse durations generate predominantly photoacoustic (stress-wave-mediated) rather than photothermal injury, producing smaller pigment fragments that are more efficiently phagocytosed by macrophages and eliminated via the lymphatic system. This mechanistic advantage—supported by electron microscopy data demonstrating smaller vacuole formation and confined pigment fragmentation with picosecond versus nanosecond lasers⁵—likely underlies the superior clearance rates and reduced PIH risk documented with picosecond platforms in several comparative studies.

For the ablative fractional CO₂ laser, the mechanism is distinct: ablative micro-channels penetrate to the papillary and reticular dermis, creating zones of controlled tissue ablation and coagulative necrosis surrounded by viable tissue. Collagen remodeling within these ablative zones may mechanically disrupt and facilitate elimination of ochronotic pigment deposits, particularly when combined with Q-switched laser treatment.

Q-switched Alexandrite Laser: Current Evidence Standard

The QS-Alex 755 nm laser represents the most direct evidence base for EO-specific treatment, primarily from the landmark case series by Bellew and Rosen (2004) and the retrospective cohort by Lazar et al. (2023).¹² The 755 nm wavelength coincides with a high melanin absorption coefficient while providing sufficient depth of tissue penetration (~2 mm) to reach papillary and mid-dermal ochronotic deposits. The case series by Bellew and Rosen (2004) is particularly notable for providing histopathological confirmation of dermal pigment reduction post-treatment, establishing a mechanistic basis for clinical improvement.

Based on the limited but consistent evidence, optimal QS-Alex parameters for EO treatment include fluences of 6.9–8.0 J/cm², spot sizes of 3–4 mm, and treatment intervals of 6–8 weeks to allow complete epidermal recovery and clearance of photoacoustically fragmented pigment particles. Simmons et al. (2015) in their comprehensive review concluded that Q-switched lasers of longer wavelengths (755 nm and 1064 nm) combined with combination laser-dermabrasion treatments showed the most significant results with minimal adverse events for EO.³

Q-switched Nd:YAG Laser

The QS Nd:YAG 1064 nm laser offers advantages over the QS-Alex system in skin of color populations due to its deeper tissue penetration (>3 mm), lower epidermal melanin absorption coefficient, and consequently reduced risk of epidermal injury and PIH. This profile makes the 1064 nm wavelength particularly valuable in FST IV–VI patients with EO who are at highest risk of PIH from lasers with shorter wavelengths.¹⁷

The split-face RCT by Mornchan et al. (2010) demonstrated that low-fluence QS Nd:YAG (1064 nm) laser treatment achieves a 92.5% improvement in relative lightness index in dermal and mixed-type melasma patients compared to 19.7% with topical hydroquinone alone, providing strong

comparative evidence for the superiority of QS Nd:YAG over conventional topical therapy in dermal pigment disorders.¹¹ These data provide the strongest RCT-level evidence for QS Nd:YAG laser in the most closely analogous condition to EO.

Picosecond Lasers: Emerging Evidence

Picosecond lasers represent the most significant technological evolution in pigmentation treatment over the past decade. The prospective split-face RCT by Ungakornpairote et al. (2020) remains the highest-quality direct head-to-head comparative evidence, demonstrating statistically significant superiority of picosecond laser over QS Nd:YAG for epidermal and dermal pigmented lesions at all follow-up time points (Week 4: $p=0.034$; Week 12: $p=0.039$; Week 24: $p=0.027$), with 85.7% of picosecond sites achieving $>50\%$ improvement at 6 months compared to 57.2% of QS sites.¹⁰

Friedmann et al. (2022) reported that three sessions of 532 nm picosecond laser achieved good-to-excellent clearance in $\geq 95\%$ of pigmented lesions with 95% patient satisfaction at 1 month.¹⁵ Evangelista et al. (2020) documented 100% complete clearance of lentigines following a single session of 670 nm picosecond laser in FST III–IV patients.¹⁴ The evaluation by Lee et al. (2025) of histologic changes following picosecond laser treatment demonstrated smaller vacuole formation with minimal surrounding damage compared to nanosecond systems, and confinement of tattoo/pigment particles within lysosomal structures—findings mechanistically consistent with lower PIH rates.⁵

Intense Pulsed Light: Role and Limitations

IPL delivers broad-spectrum filtered visible light (typically 515–1200 nm with selective filters) rather than monochromatic laser energy, enabling simultaneous targeting of multiple chromophores. Wat et al. (2014) conducted a systematic review of IPL in dermatological disease, finding Level 1 evidence for IPL in melanocytic lesions including lentigines and melasma, and Level 2 evidence for lentiginous disease.²

However, IPL is not recommended as primary treatment for EO due to its non-specific, multi-wavelength delivery that confers inadequate selectivity for deeply deposited ochronotic dermal chromophores. The comparative RCT by Wang et al. (2006) demonstrated that QS-Alex

was superior to IPL for freckle treatment ($p=0.04$), while IPL was associated with lower PIH rates for lentigines in Asian patients.¹² IPL may be considered as an adjunctive modality in EO for treating concomitant epidermal pigmentation or vascular components, but should not replace Q-switched or picosecond lasers for the primary ochronotic deposits.

Fractional CO₂ Laser

Ablative fractional CO₂ laser achieves resurfacing by generating controlled micro-ablative columns (MTZ—microthermal treatment zones) through the epidermis and into the dermis. Chen et al. (2022) provided a comprehensive review of EBD histological changes, noting that ablative lasers vaporize from stratum corneum to dermis, inducing collagen remodeling that may facilitate elimination of ochronotic deposits.¹⁷

The published combination regimens involving pulsed CO₂ laser followed by Q-switched alexandrite laser for dermal melasma (Nouri et al., 1999) provide a model for similar combination approaches in refractory EO. In a pilot study, all combination therapy patients (CO₂ + QS-Alex) achieved complete resolution versus partial response in CO₂ monotherapy patients, without scarring or infection.¹¹ However, the significantly higher risk of PIH (particularly in FST III–VI), extended downtime, and complex post-procedure management limit fractional ablative approaches to refractory EO cases where standard Q-switched monotherapy has failed.

Radiofrequency Microneedling

Radiofrequency (RF) microneedling is an emerging EBD that delivers fractional radiofrequency energy directly to the dermis via insulated microneedles, sparing the epidermis and enabling treatment in all FSTs without significant risk of PIH. Park et al. (2022) reported a prospective cohort study of pulsed-type microneedling RF for refractory facial pigmentary disorders (including Riehl melanosis and melasma) demonstrating improvement in investigator and patient global assessment, significant reduction in melanin index, and histopathological evidence of reduced melanin and melanophage density with thickened basement membrane after 5 sessions.¹³

The mechanism of RF microneedling in pigmentation disorders likely involves a combination of: (a) direct thermal injury to pigment-laden cells with subsequent phagocytic clearance, (b) collagen remodeling that may restructure the ochronotic pigment-collagen matrix,

and (c) enhanced drug delivery of topical depigmenting agents through RF-induced micropores. RF microneedling holds particular promise as an adjunctive or primary treatment for EO in highly pigmented skin types (FST V–VI) for whom even low-fluence Q-switched lasers carry significant PIH risk.

Combination Approaches

Combination EBD strategies have emerged as the most effective approach for recalcitrant EO, addressing both the deep dermal ochronotic deposits and any residual epidermal melanin components. The combination of QS-Alex laser with adjunctive microneedling (Lazar et al., 2023)² represents the most directly relevant evidence. Simmons et al. (2015) identified combination laser-dermabrasion as demonstrating the most significant results for EO.³

Broader dermal hyperpigmentation evidence supports multi-modal combination strategies. Garg et al. (2024) reported that sequential laser combinations provided substantial pigmentation reduction across all pigmentary disorder groups, with safety and efficacy maintained across FSTs.⁹ The integration of photoprotection, cessation of causative agents, topical antioxidants (ascorbic acid, niacinamide), and chemical peels as adjuncts to EBD therapy is strongly supported by pathophysiological reasoning and clinical experience, though evidence in EO specifically remains limited.

Special Considerations for Skin of Color

EO disproportionately affects individuals with skin of color (FST IV–VI), who are also at highest risk for adverse events from laser treatment, particularly post-inflammatory hyperpigmentation. This dual vulnerability necessitates careful device selection, parameter optimization, and pre/post-treatment protocols specifically designed for darker phototypes.⁴

Sowash et al. (2023) reviewed laser treatment for post-inflammatory hyperpigmentation in skin of color, concluding that Nd:YAG and fractional photothermolysis systems provide adjunctive treatment with appropriate parameters.¹⁷ The safety study by Haimovic et al. (2016) specifically evaluated the 755 nm picosecond laser with diffractive lens array (DLA) in FST IV–VI patients, reporting that adverse events (primarily transient erythema and hyperpigmentation) were mild and resolved in all cases, supporting the feasibility of picosecond platforms in deeply pigmented skin.¹⁴

Mandatory pre-treatment measures in EO patients with dark phototypes should include: (1) topical hydroquinone cessation ≥ 4 weeks before laser treatment, (2) broad-spectrum SPF 50+ sunscreen daily application, (3) test spot assessment with delayed treatment if any PIH response observed, (4) topical priming with retinoids and/or azelaic acid 4–6 weeks pre-treatment, and (5) pre-cooling and topical anesthetic application for patient comfort.

Clinical Implications

Based on the available evidence, the following clinical decision algorithm for EBD selection in EO is proposed: (1) First-line: QS-Alex 755 nm for FST I–III; QS Nd:YAG 1064 nm for FST IV–VI; (2) Second-line (refractory or FST-specific preference): Picosecond 755 nm or 1064 nm laser; (3) Adjunctive: RF microneedling for FST V–VI where laser risk is highest; (4) Combination for refractory cases: QS laser + fractional ablative; (5) Concomitant mandatory: cessation of all causative agents, strict SPF 50+ photoprotection, topical maintenance therapy.

The treatment goal in EO should be pragmatically defined as: (a) maximum achievable pigment clearance given individual patient factors, (b) maintenance of cleared areas through photoprotection and avoidance of causative agents, and (c) optimization of psychosocial QoL through restoration of uniform skin tone. Patient counseling should include realistic expectations regarding the number of sessions required (typically 4–8), the possibility of incomplete clearance, the mandatory role of long-term photoprotection, and the risk of recurrence with re-exposure to causative agents.

CONCLUSIONS AND RECOMMENDATIONS

Summary of Evidence

Exogenous ochronosis represents a challenging, treatment-resistant dermatological condition with significant psychosocial impact, primarily affecting individuals of color who have used hydroquinone-containing skin-lightening preparations. Energy-based devices constitute the most effective available interventional strategy for EO, exploiting selective photothermolysis to fragment and eliminate ochronotic pigment deposits within dermal collagen fibers.

The Q-switched alexandrite 755 nm laser provides the most direct evidence base for EO, with histopathologically confirmed dermal pigment reduction and clinically meaningful lightening

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achieved in 85–100% of patients after 4–6 sessions. The Q-switched Nd:YAG 1064 nm laser offers superior safety in darker phototypes (FST IV–VI) and is supported by high-quality RCT evidence for closely analogous dermal pigmentation conditions. Picosecond-domain laser platforms demonstrate emerging superiority in comparative RCTs for dermal pigmented lesions, with lower PIH rates that are particularly advantageous in EO patients who are predominantly skin-of-color individuals at baseline high risk for PIH. Intense pulsed light is effective for superficial epidermal components but is insufficient as monotherapy for deep dermal ochronotic deposits. Fractional CO₂ laser and radiofrequency microneedling are valuable adjunctive or second-line modalities, particularly for refractory EO.

Recommendations

Based on the synthesized evidence, the following recommendations are proposed:

- 1. Mandatory Pre-treatment:** All causative topical agents (hydroquinone $\geq 2\%$, resorcinol, phenol-containing preparations) must be discontinued a minimum of 6 weeks before initiating EBD therapy. Broad-spectrum sunscreen (SPF 50+, PA+++) should be prescribed and mandatorily applied.
- 2. Device Selection Based on FST:** QS-Alex 755 nm is recommended for FST I–III; QS Nd:YAG 1064 nm and picosecond lasers are preferred for FST IV–VI to minimize PIH risk.
- 3. Combination Therapy for Refractory EO:** Patients not responding to QS laser monotherapy after ≥ 6 sessions should be considered for combination approaches (QS laser + fractional CO₂, or QS laser + RF microneedling).
- 4. Research Priorities:** Well-designed, multicenter randomized controlled trials specifically enrolling patients with confirmed histopathological EO, using standardized outcome measures (melanin index, DLQI, physician GAS), minimum 12-month follow-up, and appropriate comparator arms are urgently needed.
- 5. Regulatory and Public Health:** Stricter regulation of hydroquinone-containing cosmetics, particularly in Sub-Saharan Africa, South and Southeast Asia, and immigrant communities in Western countries, is essential to prevent the rising incidence of EO.

6. Histopathological Confirmation: Skin biopsy should be performed to confirm the diagnosis of EO before initiating EBD therapy, as the histopathological pattern (banana-shaped ochronotic fibers) is pathognomonic and guides therapeutic decision-making.

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