Treatment of imipramine-induced hyperpigmentation with quality-switched ruby and picosecond lasers

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INTRODUCTION

Imipramine is a tricyclic antidepressant used for the treatment of mood disorders and chronic neuropathic pain. Prolonged use of this medication and other psychotropic drugs has been linked to a rare complication of slowly progressive slate-gray or brown hyperpigmentation in sun-exposed areas of skin. The most common triggers for this exogenous pigmentation are tricyclic antidepressants and phenothiazines, although cases associated with selective serotonin reuptake inhibitors, mirtazapine, and phenytoin have also been reported.[1]

Histologic examination of affected areas shows golden-brown globular deposits within macrophages in the papillary and mid dermis with positive Fontana-Masson staining and negative staining for hemosiderin and iron.[2] Electron microscopy reveals macrophages containing small cytoplasmic accumulations that can progress to 3- to 5-μm, doubly refractile granules.[3] These deposits are believed to represent drug-melanosome complexes induced by chronic photoactivation.[4] Discontinuation of the causative agent does not always result in a resolution. Furthermore, affected patients may be unwilling to discontinue the medication due to inadequate symptom control on alternative therapies. The persistence of clinically apparent hyperpigmentation can be a source of significant distress for these patients.

Topical retinoids, corticosteroids, and hydroquinone have been largely ineffective in treating this type of hyperpigmentation.[2] Only 4 reports describing laser treatment of psychotropic drug-induced hyperpigmentation were found upon review of the literature (Table I).[5-7] These cases demonstrated lightening of pigment after treatment with quality (Q)-switched ruby and Q-switched alexandrite lasers.[5-7] Picosecond-domain lasers are a relatively recent innovation in laser design approved by the US Food and Drug Administration in 2012 for tattoo removal and treatment of benign pigmented lesions.[8] This report presents a novel application of the 532-nm picosecond neodymium-doped yttrium aluminum garnet laser for the treatment of imipramine-induced hyperpigmentation.

Abbreviation used:

Q: quality

CASE REPORT

A 72-year-old woman presented to the clinic for evaluation of progressive brown and slate-gray hyperpigmentation on the face and neck. She was taking imipramine for >20 years to treat generalized anxiety disorder that failed to respond to other anxiolytics. Her daily dosage was gradually increased to a maximum of 250 mg. She first noticed hyperpigmented patches after 10 years of medication use, which eventually spread to involve the bilateral temples, cheeks, forehead, and neck at

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Table I. Summary of the literature review on laser treatment for psychotropic medication-induced hyperpigmentation

Reference	Subject(s)	Trigger	Lasers	Treatment settings	Outcome	Adverse effects
Atkin and Fitzpatrick[5] (2000)	65-year-old woman with slate-gray pigmentation of face and neck	Imipramine	Q-switched alexandrite and ruby	Full-face resurfacing with CO_2 and erbium:YAG lasers followed by 3 treatments to the forehead: ruby (6.2 J/cm^2, 4-mm spot, 74 pulses) and Q-switched alexandrite (6.0 J/cm^2, 3-mm spot, 236 pulses) ruby (8.0 J/cm^2, 4-mm spot, 115 pulses) and alexandrite (6.0 J/cm^2, 3-mm spot, 716 pulses) alexandrite laser (6.0 J/cm^2, 3 mm spot, 1017 pulses)	Partial, segmental improvement with full-face resurfacing followed by clinical and histologic clearing of pigment after final round of treatment	None reported
Wee and Dover[6] (2008)	(1) 52-year-old woman with gray-brown facial pigmentation (2) 59-year-old woman with gray-brown facial pigmentation	Perphenzine and desipramine Perphenazine and amitryptyline	Q-switched alexandrite	Three treatments with energy densities ranging from 3 J/cm^2 to 5 J/cm^2 using a 4-mm collimated spot and 50-ms pulse duration	Complete skin lightening in treated areas Progressive and incomplete skin lightening in treated areas	Temporary mild crusting, desquamation, and focal rare purpuric macules No adverse events
Izikson and Anderson[7] (2009)	69-year-old woman with bluish-gray pigmentation of dorsal aspect of hands	Imipramine	Q-switched ruby and Q-switched Nd:YAG	Two treatments with ruby (4.2 J/cm^2, 6.5-mm spot) One treatment on the left hand with Nd:YAG (6 J/cm^2, 4-mm spot)	Immediate whitening with both treatments, greater improvement with ruby laser	Polka dot bluish-gray macules developed on the area of left hand treated with Nd:YAG laser over following 3 months

Nd:YAG, Neodymium-doped yttrium aluminum garnet; *Q*, quality; *YAG*, yttrium aluminum garnet.

Fig 1. Left-side view comparison before and after a series of 3 treatments with the picosecond 532-nm laser over 17 months. Images are standardized and cross-polarized to highlight pigmentation.

Fig 2. Right-side view comparison before and after a series of 3 treatments with the picosecond 532-nm laser over 17 months. Images are standardized and cross-polarized to highlight pigmentation.

the time of presentation. Per the patient's report, a biopsy of hyperpigmented areas on the neck was obtained at another clinic, which confirmed drug-induced hyperpigmentation. The patient was diagnosed with imipramine-induced hyperpigmentation on the basis of medication history, biopsy findings, and clinical findings that were incompatible with other differential causes of photodistributed facial discoloration such as melasma and solar lentiginosis. Laser selection was determined by the patient's fair skin type and the concept of selective photothermolysis with the target chromophore of melanin. Both the 694-nm Q-switched ruby laser (SINON; Alma) and the 532-nm picosecond neodymium-doped yttrium aluminum garnet laser (PicoWay; Candela Corporation) wavelengths are well absorbed by melanin.

A series of 3 treatments with the picosecond laser was completed over 17 months (532 nm/4 mm/ 1.2-1.5 J/cm^2) to the forehead, cheeks, and temples with moderate improvement in brown hyperpigmentation (Figs 1 and 2). The patient was advised to work with her psychiatrist to taper off imipramine. She returned to the clinic after 2 months

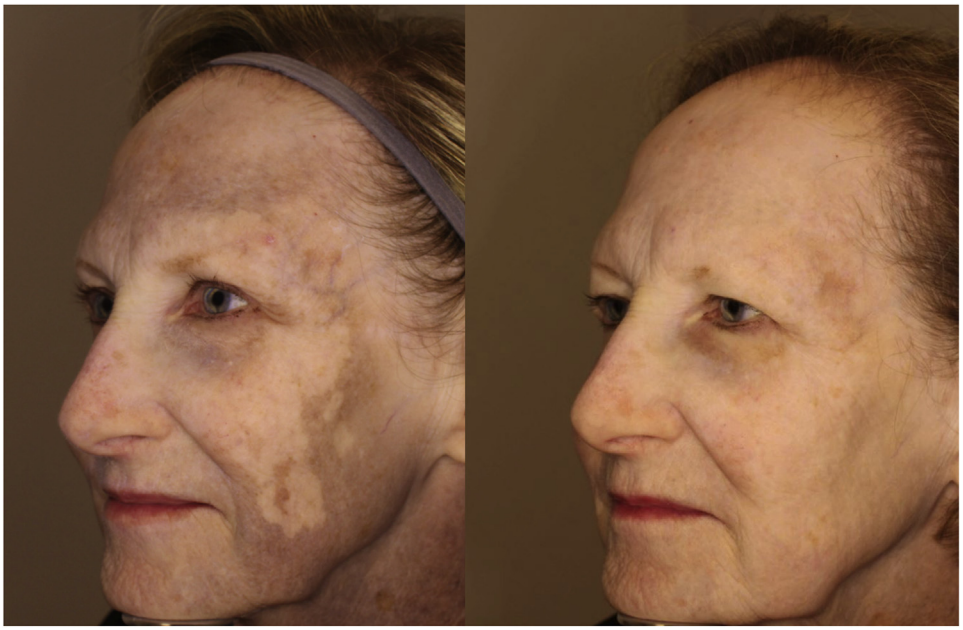

Fig 3. Left-side view comparison before and after imipramine taper, 3 treatments with the quality-switched ruby laser, and 1 final treatment with the picosecond 532-nm laser over the course of 6 months. Images are standardized and cross-polarized to highlight pigmentation.

Fig 4. Right-side view comparison before and after imipramine taper, 3 treatments with the quality-switched ruby laser, and 1 final treatment with the picosecond 532-nm laser over the course of 6 months. Images are standardized and cross-polarized to highlight pigmentation.

to begin an additional 3 rounds of treatment with Q-switched ruby laser (694 nm/5 mm/3-4 J/cm^2) and exhibited a significant reduction in slate-gray hyperpigmentation on the cheeks (Figs 3 and 4). She subsequently received 1 final treatment with the picosecond laser (532 nm/3 mm/1.8 J/cm^2) with nearly complete resolution of hyperpigmentation to the forehead, cheeks, and temples.

For pain control, topical 30% lidocaine gel was applied for 1 hour prior to the first 2 picosecond laser treatments. The patient tolerated these treatments without significant discomfort. Pronox (50% nitrous

oxide/50% oxygen mix) inhaled analgesia was used for the remainder of the picosecond and ruby laser sessions. The clinical end point for all treatments was immediate light-to-moderate frosting of pigmented areas. After each laser treatment, she experienced transient adverse effects of erythema, crusting, swelling, and darkening of treated areas. Purpura developed after 1 particularly aggressive picosecond laser session, likely due to the use of high fluences. The purpura resolved after a single session of pulsed dye laser (Vbeam Perfecta; Candela Corporation) therapy.

Although the neck was not treated with the Q-switched or picosecond lasers, some reduction in pigmentation was noted in this area due to tapering the medication. Following the courses of treatment, the patient reported that she could not tolerate discontinuing imipramine due to flares of her anxiety. She has maintained a low dose of 30 mg daily without recurrence of hyperpigmentation.

DISCUSSION

The association of photodistributed hyperpigmentation with long-term use of certain psychotropic medications is recognized; however, the consensus of management recommendations is lacking for this recalcitrant condition. The discontinuation of the offending drug is the preferred treatment. The most marked improvement was noted in our patient after she was tapered off imipramine in conjunction with Q-switched and picosecond laser treatments. However, pigmentation in some patients may not resolve for years despite medication withdrawal. Our case suggests that even a dose reduction may be beneficial for patients who cannot tolerate discontinuation of the drug.

An absence of effective topical therapies for psychotropic medication-induced hyperpigmentation has spurred the search for alternative treatment options. Since drug-melanosome complexes reside in the dermis, Q-switched lasers capable of delivering nanosecond pulses have been the preferred mode of laser therapy. Prior reports demonstrated the utility of the Q-switched ruby laser for this indication, which was supported by our experience.

Newer picosecond-domain lasers were developed to optimize the efficacy and safety of tattoo removal through the use of shorter pulse durations than nanosecond lasers. Picosecond lasers use a photoacoustic effect to fracture and disperse targeted pigment molecules with minimal photothermal damage.[8] Recent studies have demonstrated a wider variety of dermatologic applications, including treatment of melasma, photoaging, argyria, and minocycline-induced hyperpigmentation.[9,10] The reduced photothermal effect with picosecond lasers can be expected to lower the occurrence of adverse events. Picosecond pulse durations may be particularly effective for smaller cytoplasmic granules seen in this condition due to their shorter thermal relaxation time. The Q-switched ruby laser reacted best with complementary colors seen in this patient's areas of blue/gray pigmentation. Our patient experienced resolution of pigmentation over a 3-year treatment period without recurrence despite the resumption of low-dose imipramine therapy. She experienced only mild discomfort and temporary side effects due to the treatments. This regimen of combination therapy with 532-nm picosecond neodymium-doped yttrium aluminum garnet and Q-switched ruby lasers may be applicable to other cases of acquired hyperpigmentation with dermal pigment deposition composed of granules of varying sizes. Our results suggest that picosecond-domain lasers can be an important component of effective treatment regimens for this intractable skin condition.

Conflicts of interest

None disclosed.

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