Nonablative Laser and Light Therapies for Skin Rejuvenation

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Background: Multiple modalities have been described for skin rejuvenation, including ablative and nonablative therapies. Because of the prolonged recovery period associated with ablative procedures that injure the epidermis, nonablative skin treatments have grown increasingly popular. Various laser- and light-based systems have been designed or applied for promoting skin remodeling without damage to the epidermis.

Methods: Studies investigating the use of nonablative procedures for facial rhytids or acne scarring with clinical, histological, and objective quantitative measurements are systematically reviewed.

Results: Nonablative treatments are associated with clinical and objective improvements for the treatment of facial rhytids and acne scarring. Dermal remodeling seems to occur as a result of thermal injury, leading to dermal fibrosis without epidermal disruption.

Conclusions: Although results are not as impressive as those of ablative treatments, nonablative procedures are effective in the treatment of photaging and acne scarring. As technology in nonablative therapies continues to evolve, future laser and light sources may yield even more favorable results.

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ONABLA TIVE SKIN REJUVENATION, also referred to as “subsurface remodeling,” encompasses a wide spectrum of noninvasive techniques using laser, noncoherent light, or radiofrequency to improve the appearance of aging skin. Various procedures have been used to treat facial rhytids and photodamage, including dermabrasion, chemical peels, and carbon dioxide (CO2) or erbium:yttrium-aluminum-garnet (Er:YAG) laser resurfacing. These treatments promote epidermal regeneration and collagen remodeling, with excellent clinical results. However, interest in these therapies has waned significantly in recent years because of the substantial posttreatment “downtime” and prolonged recovery period. Skin resurfacing involves the destruction and removal of the epidermis accompanied by dermal contraction and remodeling. The resulting wounds require intensive skin care and have risks of adverse effects such as infection, scarring, persistent erythema, and pigmentary alteration. Growing demand for less invasive procedures with a short recuperation time that would allow minimal interruption and a quick return to daily routine has paved the way for nonablative techniques to emerge as important therapeutic options for patients. Nonablative modalities obviate the need for epidermal injury and promote the reorganization and increase of important dermal structures to reverse photoinduced aging of the skin via thermal or photochemical processes. This review discusses the available technological advancements in facial rejuvenation that improve the appearance of photodamage without wounding the epidermis while minimizing the recovery period.

Photodamage is premature aging of the skin caused by repeated sun exposure. Photodamage manifests as rhytids, pigmentedary changes, laxity, skin coarseness, and roughness. In contrast, chronological skin aging results in thin skin with diminished elasticity, but skin that is smooth and evenly pigmented. UV irradiation leads to dermal damage and is evidenced as disorganized collagen fibrils and abnormal elastic material histologically. Repeated sun exposure is accompanied by elevations in matrix metalloproteinases and collagen degradation, and may lead to persistent breakdown of dermal elements. These alterations in collagen organization contribute to the skin laxity and wrinkling seen in photo-

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toddamaged skin. Long-term studies examining the histological changes after CO₂ and Er resurfacing have been predominantly confined to the dermis, with extensive collagen and elastic fiber reorganization. The significance in these microscopic findings lies in their correlation with clinical improvement of rhytids, suggesting that dermal remodeling rather than epidermal ablation is largely responsible for wrinkle reduction and that epidermal removal may not be necessary. On the basis of these results, it is believed that promoting dermal collagen remodeling with nonablative laser treatments can improve the clinical manifestations of photoaging, including facial rhytids, texture, and tone.

In addition to rhytids, nonablative lasers can be used to improve a whole spectrum of skin problems, including vascular anomalies, pigmented lesions, hypopigmentation, acne vulgaris, acne scarring, unwanted hair, skin laxity, and actinic keratoses. There are numerous laser, light, and radiofrequency devices used for these purposes. They include lasers emitting light in the visible and infrared range. Laser systems emitting wavelengths in the visible range include potassium-titanyl-phosphate (KTP) and diode lasers (532 nm), pulsed-dye lasers (PDLs) (585-595 nm), diode lasers (810 and 980 nm), and alexandrite lasers (755 nm). Longer-wavelength systems emitting infrared light include the Q-switched Nd:YAG (1064 nm), long-pulsed Nd:YAG (1064 and 1320 nm), diode (1450 nm), and Er:glass (1540 nm) lasers. The intense pulsed light systems (IPLs) emit noncoherent light that ranges from 500 to 1200 nm based on the application of different filters. Other new innovations that promote facial rejuvenation include monopolar and bipolar radiofrequency devices, light-emitting diodes (LEDs), and fractional laser treatments.

As with many advances in medicine, the initial discovery of applying nonablative technology for rhytid reduction came as a serendipitous observation. An area where a vascular lesion was previously treated with a PDL had improvement in rhytid appearance. Subsequent reports using the PDL confirmed these initial findings. Although there still remains much to be elucidated about the precise mechanism of action of nonablative technology, important factors have been distilled from the existing data. “Spatially selective photocoagulation” is a term used to refer to the process of epidermal sparing and selective thermal injury of the dermis, and aptly describes nonablative laser treatments. Key components to nonablative rejuvenation are epidermal sparing and proper selection of laser irradiation wavelength and energy to evoke the desired thermal response in the papillary and upper reticular dermis. Depth of thermal injury should be limited to 100 to 400 μm below the epidermis, the area where most solar elastosis is seen histologically. Epidermal protection can be accomplished by cryogen spray or contact cooling. By cooling the skin, thermal injury can be confined to the papillary and upper reticular dermis. One should avoid heating the epidermis to temperatures above 60°C to 65°C, the threshold for epidermal denaturation. Heating the dermis causes collagen denaturation and fibroblast stimulation via an inflammatory cascade, leading to neocollagenesis.

### PULSED-DYE LASER

Lasers targeting oxyhemoglobin, such as the PDL (at 585-595 nm), can be applied to heat dermal vasculature and adjacent perivascular collagen, prompting an inflammatory response, cytokine release, and collagen remodeling. Zelickson et al described the application of the PDL (585 nm) for stimulation of fibroblasts and new collagen formation in periocular skin. Twenty patients underwent one treatment with a 585-nm 450-microsecond PDL. Fluence ranged from 3.0 to 6.5 J/cm², with a 7- or 10-mm spot size. Of 10 patients with mild to moderate rhytids, 9 had at least 50% improvement, based on assessments by 3 evaluators. These patients maintained their improvement at the 6-month follow-up visits. Among the 10 subjects with moderate to severe rhytids, 3 had clinical improvement. Light microscopic examination of treated areas demonstrated thickened collagen. Ultrastructural analysis showed active fibroblasts and a reduction in degenerated elastic fibers. However, there was significant postprocedure purpura and edema that lasted 1 to 2 weeks, making this less attractive for patients seeking facial rejuvenation with minimal downtime.

Further investigations were conducted using low-energy PDLs such that blood vessels remained intact with no resultant purpura. Bjerring et al treated 30 patients with a modified 585-nm PDL and a pulse duration of 350 microseconds (N-Lite; ICN Photonics, Costa Mesa, Calif). A fluence of 2.4 J/cm² was delivered using a 3-mm spot size. None of the subjects developed purpura or pigmentation changes. A statistically significant increase in propeptide type III procollagen was measured. A clinical evaluation 6 months after one treatment found 52% of the improvement seen in prior CO₂ studies for class I rhytids, 89% of the improvement for class II rhytids, and 79% of the improvement for class III rhytids. A subsequent study using the same system, however, failed to yield such favorable results. Hohenleutner et al treated 12 patients with moderate and severe rhytids at a fluence of 2.5 J/cm². At 2- and 4-month follow-ups, there was no improvement in rhytids, per patients’ and physicians’ assessments. At the 6-month visit, one patient reported mild improvement.

In another study using the short-pulse PDL, 10 subjects with mild to moderate rhytids were treated twice at 1-month intervals. One nonoverlapping pass of the 585-nm laser (pulse duration, 350 microseconds; fluence, 2.5 J/cm²; and 5-mm spot size) was performed. Electron microscopy of pretreatment and adjacent skin biopsy specimens 6 months after the first treatment showed changes suggestive of new collagen formation. Long-pulse PDLs have also been studied for photorejuvenation benefits. Four monthly treatments with the long-pulse 595-nm PDL (Vbeam; Candela Corp, Wayland, Mass), at 6 J/cm², with a 10-mm spot size, a pulse duration of 6 milliseconds, a cryogen spurt duration of 20 milliseconds, and a delay of 30 milliseconds, were administered on one cheek. The other cheek was treated with cryogen spray alone. Among the 15 treated patients, 11 showed improvement on the laser-irradiated cheeks, based on blinded observer assessments. They had an average improvement of 18.1%. Three patients showed improvement on the cryogen-treated cheeks. One subject had no improvement on either cheek.
The long-pulse 595-nm PDL was studied at various subpurpuric doses. Ten subjects with class II and III rhytids were divided into 2 treatment groups: one group received one treatment, and the second received 2 treatments at 1-month intervals. Each patient was treated on one side of the face using the following settings: fluence, 5 to 6 J/cm²; pulse duration, 1.5 milliseconds; and spot size, 7 mm. The contralateral side was treated at the following settings: fluence, 8 to 11 J/cm²; pulse duration, 40 milliseconds; and spot size, 7 mm. Seven subjects had mild to moderate improvement 6 months after treatment. Six subjects noted equivalent improvement on both sides of the face. No difference was noted between the single- and double-treatment areas. No significant difference was seen histologically among the different treatment sites. Ultrastructural analysis demonstrated thicker type I collagen in posttreatment specimens in all patients.

A comparative histological study of the CO₂ laser and the 595-nm PDL was undertaken using a porcine model, a model most reliable in simulating human skin in dermal injury response and collagen formation. Twenty-four combinations of energy fluences, ranging from 4 to 7 J/cm², with pulse durations ranging from 1.5 to 20 milliseconds, and a 7- or 10-mm spot size, with and without cryogen spray, were applied. Adjacent skin treated with the CO₂ laser served as a positive control, and non-cryogen spray, were applied. Adjacent skin treated with higher fluences, a larger spot size, and longer pulse durations resulted in increased collagen band width and cellular hypertrophy. The presence or absence of cryogen cooling did not affect the dermal response. However, pigmentary incontinence was seen in the non-cryogen cooling and CO₂-treated skin specimens, as expected. Objective measurements to demonstrate dermal changes after irradiation with PDL treatments showed increased collagen after one treatment. Ten patients with facial rhytides were treated in a session with the 585-nm PDL (N-Lite), an energy fluence of 2.4 to 3.0 J/cm², a spot size of 5 mm, and a pulse duration of 350 microseconds. Ultrasonographic measurements obtained at baseline and at 30 and 90 days after treatment showed an increase in dermal collagen.

Atrophic scars have also improved with the treatment of PDLs. Ten patients with mild to moderate atrophic or punched-out acne scars on the cheeks were treated with one session of a 585-nm PDL. Settings included a pulse duration of 350 microseconds, a fluence of 1.9 to 2.4 J/cm², and a 5-mm spot size. Patients were examined at 30, 60, 90, and 120 days after the procedure. Sili-cone models were obtained at baseline and at the 60-day follow-up, and an optical profilometer was used for analysis. Patient self-examination at the 60-day visit reported slight improvement in 3 patients, moderate improvement in 5, and excellent improvement in 2. Observers at the 120-day visit found 4 patients with slight improvement, 6 with moderate improvement, and none with excellent improvement. Surface profilometry showed a statistically significant reduction of 47.8% in scar depth after the single laser treatment. One case of transient purpura that resolved in 2 days was reported.

**FREQUENCY-DOUBLED KTP 532-nm Nd:YAG LASER**

Given the good absorption of dermal vessels, the 532-nm KTP laser has been investigated for potential nonablative benefits. Eleven women with mild to deep perioral rhytids were treated with a 532-nm KTP laser (VersaPulse; Lumenis Inc, Santa Clara, Calif) on one side of the perioral region. Fluence ranged from 4 to 7 J/cm², with a 2-millisecond pulse duration and a 3-mm spot size. An average of 3 treatments every 3 to 6 weeks was administered. A blinded observer identified the treated side correctly in 8 of the 11 patients. Patient self-assessments showed an average improvement of 51.4%.

Another study evaluating the use of the 532-nm laser for photorejuvenation involved the long-pulse 532-nm diode laser (DioLite Laser; Iridex Corp, Mountain View, Calif) with a scanner (ScanLite; Iridex Corp). Eight patients were treated on half of their faces, with the other side serving as a control. A fluence range of 10 to 14 J/cm² and a pulse duration from 13 to 17 milliseconds was used. Of 7 subjects, 5 had noticeable improvement according to blinded observers. An overall improvement of 29% was seen in the laser-irradiated areas.

Not all studies have demonstrated efficacy. A split-face comparison study examining the long-pulse 532-nm KTP laser (at 7 J/cm², 2 milliseconds, and 4 passes) and the 585-nm PDL (at 2.5 J/cm², 0.45 millisecond, and a single pass) on moderate to severe periorbital rhytids yielded no improvement based on patient self-assessment. Seven patients were treated. Three treatments were administered at 6-week intervals.

**980-nm DIODE LASER**

Preliminary work examining the potential role of the 980-nm diode laser as a nonablative modality has been reported. By using a 25-W diode laser (SkinLaser; BioLase Technology, Inc, San Clemente, Calif), in vivo testing on eyelid skin in 2 patients before blepharoplasty was compared with 3 passes with the scanned CO₂ laser. Treatment settings included a power range from 6 to 24 W and a 400-millisecond pulse duration. Air cooling protected the epidermis. Tissue shrinkage of 16% along with epidermal preservation with the diode laser was evident compared with 15% shrinkage seen in CO₂ laser treatment, suggesting that dermal effects may be obtained using the diode laser in a less invasive manner compared with the CO₂ laser. Additional work is needed to clarify this further.
Q-SWITCHED Nd:YAG LASER

The Q-switched Nd:YAG laser emits a 1064-nm wavelength beam that targets water within the papillary and reticular dermis and is believed to promote collagen remodeling through selective thermal injury of dermal elements. The short pulse duration in the nanosecond range is thought to confine injury to the intended target and minimize heat diffusion to other structures. To our knowledge, this was the first laser system examined for nonablative application. An early study examining its benefits as a nonablative modality on facial rhytids involved a comparison study of 11 patients between the scanned and pulsed CO\textsubscript{2} laser and the 1064-nm Q-switched Nd:YAG laser.\textsuperscript{30} By using a 3-mm spot size and a fluence of 5.5 J/cm\textsuperscript{2}, perioral and periorbital rhytids were treated. Three patients had results comparable to those of the CO\textsubscript{2} laser, 6 had some improvement, and 2 had no improvement. Erythema lasted up to 3 months in patients. A disadvantage of this modality in this early study was the resultant pinpoint bleeding.

A subsequent study investigated the use of a Q-switched Nd:YAG laser with a topical carbon suspension. The addition of a carbon suspension was to provide a chromophore target to enable the use of a lower fluence and to reduce epidermal damage. Four treatments at 7- to 10-day intervals at 2.5 J/cm\textsuperscript{2}, using a 6- or 7-mm spot size, were administered to 12 patients. An average of 25% improvement was seen. Two patients with type VI skin had focal areas of temporary hypopigmentation.\textsuperscript{31}

Another group used similar settings (7-mm spot size, fluence of 2.5 J/cm\textsuperscript{2}, and a 6- to 20-nanosecond pulse duration) to deliver 3 treatments at 4-week intervals. At least slight improvement of 97% of class I and 68% of class II rhytids was observed.\textsuperscript{32}

Objective measurements to quantify the improvements seen with the Q-switched Nd:YAG laser have been used with a 3-dimensional microtopography system (PRIMOS; GFM, Teltow, Germany). By using the Q-switched Nd:YAG laser (Medlite IV; Continuum, Santa Clara) with a spot size of 6 mm and a fluence of 3 to 3.5 J/cm\textsuperscript{2}, multiple passes were performed in the periorbital and perioral area to a clinical end point of erythema. At a follow-up visit 6 months after the fifth treatment, a 26% reduction in skin roughness was found, correlating with the clinical and subjective response of 25% to 50% improvement. These patients continued to improve at subsequent follow-up visits up to 3 months following their last treatments, suggesting that collagen reorganization was ongoing beyond the last treatment.\textsuperscript{33}

### 1320-nm Nd:YAG LASER

The 1320-nm Nd:YAG laser system (CoolTouch; New Star Lasers, Roseville, Calif) has been specifically designed for nonablative resurfacing. Epidermal protection is provided by cryogen cooling. The initial study by Nelson et al reported its use with fluences up to 10 J/cm\textsuperscript{2} and a 5-mm spot size. A clinical improvement in 60% of periorbital rhytids was seen, along with the replacement of haphazardly arranged collagen fibrils with organized collagen bands histologically.\textsuperscript{34} Subsequent studies have noted similar improvements in facial rhytids. Another early study with the 1320-nm Nd:YAG laser for facial rhytids consisted of 10 subjects with class I to III rhytids who were treated in 4 sessions. All subjects demonstrated new collagen formation in the papillary dermis, while 8 showed subjective improvement in their skin.\textsuperscript{35}

By using a cryogen cooling system, spatially selective photocoagulation was achievable with epidermal protection.\textsuperscript{36} Thirty-five subjects with periorbital rhytids were treated with a 1320-nm Nd:YAG laser (New Star Lasers) in combination with cryogen spray cooling in 3 sessions at 2-week intervals. Cryogen spray, for 20 to 40 milliseconds with a 10-millisecond delay, was followed by laser delivery of 28 to 36 J/cm\textsuperscript{2}, with a 5-mm spot size. Assessment at 12 weeks after the last treatment showed statistically significant improvements in mild, moderate, and severe rhytids. At 24 weeks, only severe periorbital rhytids showed a statistically significant improvement.

Full-face treatment for dermal remodeling with the Nd:YAG laser was studied. Five treatments were administered at 3- to 4-week intervals using a fluence range between 30 and 40 J/cm\textsuperscript{2} as a macropulse consisting of 3- to 300-second micropulses, with a 5-mm spot size. Cryogen cooling spray was delivered for 30 milliseconds, with a delay time of 40 milliseconds before the laser pulse. An independent observer determined at 6 months following the last treatment that all patients had some degree of improvement. Histological analysis demonstrated new collagen formation in all posttreatment biopsy specimens.\textsuperscript{36}

Another pilot study looked at the application of the 1320-nm Nd:YAG laser for focal rhytids, using a 5-mm spot size, a 300-microsecond pulse duration delivered at 100 Hz as a 20-millisecond macropulse, a fluence of 32 J/cm\textsuperscript{2}, and a cryogen spray of 20 milliseconds with a 10-millisecond delay. After 3 treatments at 2-week intervals, only 4 of the 10 subjects treated had mild improvement that was not statistically significant. Three patients had small increases in dermal collagen in posttreatment biopsy specimens, and 1 had a slight decrease. Adverse effects in the study were hyperpigmentation in 4 patients that lasted 1 to 3 months and several 2-mm pitted scars preceded by blistering in the treatment sites in 3 patients.\textsuperscript{37} The disappointing results may be attributable to the short follow-up period (3 months), which may not have been long enough to see the full benefit of clinical and histological findings.\textsuperscript{36}

A 1320-nm Nd:YAG laser with a built-in dynamic thermal sensing device to detect and prevent laser firing if epidermal temperatures fall out of the 32°C to 34°C range was studied for the treatment of acne scarring (CoolTouch II; New Star Lasers). Eight patients with mild to severe acne scarring were treated with the 1320-nm diode laser at 13 to 18 J/cm\textsuperscript{2}, with a 10-mm spot size and 6 stacked 350-microsecond pulses, forming a 50-millisecond macropulse. Three passes were administered. The first 2 passes were in a precooling mode, in which 30 milliseconds of cryogen was delivered 10 milliseconds before laser irradiation and the fluence ranged from 14 to 18 J/cm\textsuperscript{2}. The final pass was in a postcooling mode, in which 30 milliseconds of cryogen was delivered 10 milliseconds after laser irradiation and the fluence ranged from 13 to 17 J/cm\textsuperscript{2}. A total of 6 treatments were performed at 4-week intervals. Non-
treating observers compared photographs taken at baseline, at 5 months, and at 1 year after the first treatment. Seven patients had improvement at the 5-month visit. Ice pick scars without fibrous tracts responded most favorably compared with punched-out scars and ice pick scars with fibrous tracks. Observer assessment noted a statistically significant improvement of 20% to 39% at the last treatment and 40% to 59% at the 1-year visit (5 months after the last treatment). Patient assessment at the last treatment demonstrated a statistically significant improvement of 20% to 39%. The most recent 1320-nm Nd:YAG laser (CoolTouch III; New Star Lasers) has precooling, midcooling, and postcooling modes that enhance pain tolerance (Figure 1).

1540-nm Er:GLASS LASER

The Er:glass 1540-nm laser is a flashlamp-pumped system with a codoped ytterbium-Er:phosphate glass material and an optic fiber whose emitted wavelength has a high water absorption and a low melanin absorption. The midinfrared emission penetrates to depths of 0.4 to 2 mm. Ross et al investigated the utility of the Er:glass laser for skin remodeling. Nine patients were treated with a flashlamp-excited Er:glass laser (Candela Corp). Seven postauricular sites were treated on each patient: 4 on one side and 3 on the contralateral side. One side was assigned 1 pass and the other side received 2 passes of laser irradiation. Energy ranged from 16 J/cm² (8 pulses of 2 J/cm²) to 144 J/cm² (48 pulses of 3 J/cm²); there was a 5-mm spot size and a pulse width of 1.2 milliseconds. A sapphire chill tip was applied to the skin for surface cooling. Six sites were followed up for 2 months after treatment. A biopsy was performed on the rest immediately after treatment. There was clumping of collagen and elastin, with a mean depth of injury at a 703- and 518-μm band of altered collagen in areas immediately posttreatment. Dermal fibroplasia was seen at 2 months posttreatment, and measured an average of 980 μm from the top of the epidermis, with an average thickness of 760 μm. However, there was no clinical improvement. Immediate skin whitening and subsequent scarring were seen at sites treated with a fluence of greater than 60 J/cm². The settings that were used in this study seemed to cause excessive injury, altering collagen at a greater depth, with resultant depressions and skin lightening. It was suggested that the depth of thermal injury be restricted to the superficial dermis to effect clinical change.

A subsequent study examining different equipment settings and clinical effects on rats showed a definite dose- and temperature cooling–dependent relationship. Unlike single-pulse emissions that lead to epidermal injury, pulse train irradiation demonstrated epidermal protection and thermal damage confined to the upper dermis, with neocollagenesis. Levy et al undertook a dose-response study to determine the maximum number of pulses needed to treat periorbital and perioral skin safely using the 1540-nm Er:glass laser (Aramis laser; Quantel Medical, Clermont-Ferrand, France). Ten patients were treated with an increasing number of pulses, from 3 to 8, for a total energy of 24 to 64 J/cm². Adverse effects were documented at the 3-month follow-up visit. Adverse effects included hyperpigmentation in 2 patients, textural changes in 2, and pitted scars in 3. The periorbital area was especially
sensitive to dermal heating. The researchers concluded that optimal settings were as follows: for the periorbital region, 3 pulses (at 24 J/cm²); and for the perioral area, 5 pulses (at 40 J/cm²).

Fournier et al studied the effect of this laser on perioral and periorbital rhytids quantitatively using profilometry with silicone imprints, ultrasonographic imaging, and histological analysis. With a sapphire tip for contact cooling, laser irradiation treatment settings were 24 J/cm², 2 Hz, and a 4-mm spot size for periorbital rhytids and 40 J/cm², 2 Hz, and a 4-mm spot size for periorbital rhytids. Forty-two patients received 5 treatments 6 weeks apart. silicone imprints were completed at baseline, at 12 weeks, and at 24 weeks. Ultrasonographic imaging results were obtained at baseline, at 1 week after the third treatment, and at 3 weeks after the third treatment. Ultrasonographic imaging showed an increase of 17% in dermal thickness 18 weeks after the first treatment. Silicone imprints demonstrated progressive improvement in anisotropy (an indicator of collagen orientation in which values increase with increasing extrinsic age) after successive treatments. Preauricular biopsy specimens of treatment areas 2 months after the last treatment demonstrated slightly thickened collagen bands in the superficial dermis and rearrangement of the collagen fibers in a more horizontal manner, correlating with clinical improvements seen after treatment.

A follow-up report by Fournier et al published results of ultrasonographic imaging and silicone imprints obtained at 14 months after initial enrollment. Silicone imprinting from 14 patients at follow-up showed a persistent reduction in anisotropy, with greater changes observed in the periorbital area compared with the perioral region. Dermal thickness, measured by ultrasonographic imaging, persisted over time in the 4 patients seen at follow-up. An increase of 11% was noted, compared with the 17% increase seen 18 weeks after the first treatment. A slight reduction, the researchers proposed, was expected because of the horizontal rearrangement of new collagen fibers that occurs with collagen remodeling.

Another series of 24 patients with mild to moderate periorbital and perioral rhytids was treated with the 1540-nm Er:glass laser followed by histological evaluation. Three treatments at monthly intervals were administered at a fluence between 30 and 40 J/cm² (10 J/cm² per pulse, with 3-4 pulses), at 2 Hz, with a 4-mm spot size and a 3.5-millisecond pulse duration, using a 1540-nm Er:glass laser (Aramis laser). Surface cooling was accomplished with a sapphire lens chilled to 5°C. Standardized photographs were obtained before treatment, immediately after the first treatment, and at 1, 3, and 6 months after the final treatment. Patient self-examination and blinded observer assessments showed mild to moderate clinical improvement in the periorbital and perioral regions. Skin biopsy specimens were obtained at baseline, after the first treatment, and at the 1- and 6-month follow-up visits. Tissue edema and acute inflammation were seen in specimens from immediately irradiated areas. The 6-month follow-up biopsy specimen showed mild dermal fibroplasia.

Application of this laser (Aramis laser) for the treatment of neck lines and rhytids on the forehead has been investigated. Twenty subjects received 5 treatments at 1-month intervals. Measurement of skin thickness of the neck and forehead using ultrasonographic imaging and of mechanical properties of the forehead using an echorhonometer was conducted at baseline, 1 month after the third treatment, 1 month after the fifth treatment, and 3 months after the fifth treatment. Each treatment consisted of 3 pulses (30 J/cm² cumulative fluence), a 2-Hz repetition rate, a 4-mm spot size, and a contact cooling system for epidermal protection. No acute or latent adverse effects were reported. All patients reported 10 of 10 for overall satisfaction 3 months after the last treatment. Patients scored 8 for neck skin tone, 9 for forehead skin tone, 6 for forehead skin texture, and 5 for neck skin texture. A photographic evaluation demonstrated a mild global improvement of treatment areas. There was a statistically significant increase in dermal thickness observed as a function of time in the neck (mean±SD, 1.42±0.14 mm preoperatively vs 1.53±0.11 mm 3 months after the fifth treatment) and forehead (mean±SD, 1.79±0.19 mm preoperatively vs 1.86±0.18 mm 3 months after the fifth treatment). Skin firmness on the forehead also demonstrated a statistically significant improvement as a function of time (mean±SD, 7.62±3.68 kPa preoperatively vs 16.68±7.44 kPa 1 month after the fifth treatment).

1450-nm DIODE LASER

The 1450-nm diode laser is a mid–infrared wavelength laser that penetrates to a depth of about 500 µm. Peak powers are in the range of 10 to 15 W, and pulse durations range from 150 to 250 milliseconds. Epidermal cooling is provided by cryogen spray.

To address the question of whether the improvements seen in nonablative therapy are attributable to the laser itself or to nonspecific physical trauma, a split-face study examining the effect of the 1450-nm diode laser (Candela Corp) compared with cryogen alone was performed. Twenty patients with class I to II rhytids were treated in 2 to 4 treatment sessions, with a 6-month follow-up. Patients were treated with the laser and cryogen spray on one side of the face. The contralateral side was treated with cryogen spray only. Seven subjects showed no improvement, 10 had mild improvement, and 3 had moderate improvement on the laser-treated side. The cryogen-treated side reflected no improvement.

Additional studies have reported rhytid improvement with the 1450-nm diode laser. Tanzi et al evaluated the efficacy of the 1450-nm diode laser for the treatment of facial rhytids in a split-face controlled study. By using a fluence range of 15 to 20 J/cm² (average, 17.5 J/cm²), a 4-mm spot size, a pulse duration of 210 milliseconds, and a dynamic cooling device set at 10 milliseconds for precooing, 30 milliseconds for intracoooling, and 20 milliseconds for posttreatment cooling, a single pass of nonoverlapping pulses was delivered. Four consecutive treatments were administered at 3- to 4-week intervals. Clinical end points were mild erythema and edema without vesiculation. A clinical evaluation demonstrated modest improvements in the treated areas. Improvements peaked at the 6-month follow-up visit. The 12-month visit revealed no additional benefit. A histo-
logical examination noted new collagen formation in the treated areas. Adverse effects included temporary redness, swelling, and postinflammatory hyperpigmentation. Postinflammatory hyperpigmentation resolved with topical hydroquinone therapy within 4 to 21 weeks. Consistent with other nonablative studies, periorbital rhytids were more responsive than perioral rhytids.

A subsequent split-face study compared the use of the 1450-nm diode laser with the 1320-nm Nd:YAG laser for the treatment of atrophic scars.48 Twenty patients with mild to moderate atrophic facial scars received 3 treatments. On the diode laser–treated side, patients received one pass of nonoverlapping laser pulses. The fluence ranged from 9 to 14 J/cm² (average, 11.8 J/cm²), with a 6-mm spot, 10 milliseconds of precooling, 30 milliseconds of intraoperative cooling, and 10 milliseconds of postcooling. Using the 1320-nm Nd:YAG laser, energy delivery ranged from 12 to 17 J/cm² (average, 14.8 J/cm²), with a 10-mm spot size and a skin surface temperature between 39°C and 45°C. Two passes in a non–pulse-stacking fashion were administered. Clinical response, histological evaluation, and objective measurements using the 3-dimensional in vivo microtopography imaging system were assessed. Clinical improvement was seen maximally at the 6-month follow-up visit after the last treatments. Higher clinical scores were seen with the 1450-nm diode laser–treated side of the face. Histological analysis demonstrated increased collagen in the 6-month follow-up biopsy specimens. No new collagen was noted in the 12-month follow-up specimens. Interestingly, 3-dimensional microtopographic imaging analysis demonstrated decreased skin roughness at 6 months that persisted in the 12-month follow-up visits. Adverse effects included postprocedure erythema observed 24 hours after treatment with the 1450-nm diode laser and 6 hours after treatment with the 1320-nm laser. Postinflammatory hyperpigmentation was observed in 7% of the 60 treatment sessions with the 1450-nm laser and 3% of the 60 sessions with the 1320-nm laser. There was no hypopigmentation or hypertrophic scarring observed. The 1450-nm laser–treated side received higher mean patient satisfaction scores (5.7 vs 4.6). A criticism of this study is the use of subtherapeutic treatment settings with the 1320-nm laser. Multiple passes, especially for acne scar improvement, have been well tolerated and quite effective.

**IPL Device**

Intense pulsed light is a noncoherent filtered flashlamp that emits broadband light in the visible and infrared spectrum, ranging from 500 to 1200 nm. It is useful in the treatment of lentigines and telangiectases and in tattoo removal. Multiple reports have described the benefits of IPL therapies for nonablative rejuvenation. One of the early studies reporting its efficacy in rhytid reduction involved 49 patients who completed 4 to 6 full-face treatments (average, 4.94) at 3-week intervals. Cutoff filters of 550 or 570 nm were used. Treatment fluences ranged from 30 to 50 J/cm², and energy was delivered in double- or triple-pulse trains of 2.4 to 4.7 milliseconds and pulse delays of 10 to 60 milliseconds. All patients reported some degree of improvement in wrinkles, and 45.5% reported at least 50% improvement in rhytids. Nearly 72% reported a 50% or greater improvement in skin texture and smoothness. Of the patients, 67% also reported at least a 50% improvement in the appearance of their pores. As expected, improvements in facial erythema and telangiectasia were also observed. A pretreatment and posttreatment biopsy specimen demonstrated new collagen formation in the papillary and reticular dermis.49 Another group described a series of 30 subjects with class I to II facial rhytids who underwent IPL treatments (ESC Medical, Yokneam, Israel) with a 645-nm cutoff filter.50 Most underwent 3 or 4 treatments at 2-week intervals. Energy ranged from 40 to 50 J/cm². Triple 7-millisecond pulses with a 50-millisecond delay in between were delivered. Six months after the last treatment, 9 subjects showed substantial improvement, 16 had some improvement, and 5 had no improvement. All subjects had some degree of erythema after treatment. Three had blistering after at least one treatment session. There were no residual pigmentary changes, scarring, or erythema noted at the 6-month follow-up.

Another study examined 5 patients with mild photodamage who were treated monthly for 5 treatments using a 560-nm filter, an 8 × 35-mm spot size, and a fluence range of 28 to 36 J/cm² with the IPL instrument (Quantum SR; ESC-Lumenis, Norwood, Mass). Energy delivery consisted of a double pulse of 2.4 and 4.2 milliseconds and a pulse delay of 15 milliseconds. A unique finding of this study was the diminished concentration of Demodex organisms and the accompanying perifollicular inflammation seen under light microscopy, suggesting an anti-inflammatory mechanism to help account for the clinical benefits seen. The collagen remained unchanged.51

A retrospective medical record review of 80 patients treated with IPL from 1996 to 1997 on the face, neck, and chest was reported.52 The IPL system used (Photoderm VL; Lumenis) had 550- to 590-nm cutoff filters. The 570-nm filter was most commonly used. Some patients were treated with single pulses with 2.4- to 3-millisecond durations. However, most were treated with double pulses, with a 2.4-millisecond duration, a 10-millisecond delay, and then a 6.0-millisecond duration. Double pulsing with an initial short pulse and then a longer pulse was effective, with fewer adverse effects. With greater pigmentation, a 550-nm filter was used along with a double pulse, with a 2.4-millisecond duration, a 10-millisecond delay, and a 4-millisecond duration. Fluence ranged from 22 to 28 J/cm² for a single pulse and from 30 to 44 J/cm² for double pulses. Based on photographs and patient self-assessments, skin texture improvement was observed in 82% of the patients 4 years following treatment. The median number of treatments was 3. The face had the greatest long-term improvement—90% had improved texture, fewer telangiectases, and less dyschromia. The chest had 76% improvement, and the neck had 71% improvement. Adverse effects were rectilinear hypopigmentation in focal areas, especially the neck region, lasting 6 to 12 months in 2.5% of the patients. One patient had residual hypopigmentation still present at the 4-year follow-up. Temporary crusting lasting 1 to 3 days was seen in 19% of the patients, purpura resolving within 1 to 5 days was seen in 6%, and transient hyperpigmentation and mild facial edema, lasting 1 to 3 days, was seen in 17%.
LONG-PULSE Nd:YAG LASER

The long-pulse Nd:YAG laser emits energy in the infrared spectrum at a wavelength of 1064 nm with extended pulse durations. Diffuse heating of dermal tissue at the 1064-nm wavelength penetrates to depths of 5 to 10 mm and permits slow heat diffusion with low energy absorption by melanin. In one study, 34 patients completed at least 7 treatments using the long-pulse Nd:YAG laser (Lyra; Laserscope, San Jose, Calif). Skin types I through V were treated at 22 J/cm², with a 50-millisecond pulse width, using a 10-mm spot size. A contact cooling device provided epidermal protection. Three passes were administered over the full face. Treatments were repeated weekly. By using photographic documentation, statistically significant improvements in coarse and fine wrinkles and skin laxity were found in all patients based on masked objective analysis of pretreatment and posttreatment photographs by 3 evaluators. Similarly, self-assessments by the subjects also reported improvements in facial rhytids. No significant adverse events were noted.54

A study comparing the use of the long-pulse 532-nm KTP laser (Aura; Laserscope) with the 1064-nm Nd:YAG laser (Lyra) alone or the combination of the 2 lasers for skin rejuvenation was recently reported.55 One hundred fifty patients with skin types I through V were treated (50 in each treatment group). Fluences ranged from 7 to 15 J/cm² at a 7- to 20-millisecond pulse duration with a 2-mm handpiece, and from 6 to 15 J/cm² at a 30- to 50-millisecond pulse duration with a 4-mm handpiece, for the KTP laser. For the Nd:YAG laser, fluences ranged from 24 to 30 J/cm² with a 10-mm handpiece, and were 30 J/cm² for a scanner (SmartScan Plus) at 65-millisecond pulse durations. Patients were treated 3 to 6 times at monthly intervals. In the KTP laser-alone treatment group, there was a 30% to 40% improvement in skin texture, a 30% to 50% improvement in skin tone/tightening, and a 70% to 80% improvement in redness and pigmentation. The Nd:YAG laser treatment group had a 10% to 20% improvement in redness, a 0% to 10% improvement in pigmentation, a 10% to 30% improvement in wrinkles, and 60% to 80% patient satisfaction. The combination group showed a 70% to 80% improvement in redness and pigmentation, a 40% to 60% improvement in skin tone/tightening, a 40% to 60% improvement in skin texture, a 30% to 40% improvement in wrinkles, and a 80% to 100% patient satisfaction. The posttreatment follow-up was up to 18 months after the last treatment. The combination of the KTP and Nd:YAG lasers was more effective than either of the lasers alone.33

LIGHT-EMITTING DIODES

Light-emitting diodes emit narrow bands of low-intensity light ranging from UV to visible to infrared. It is theorized that cellular receptors are activated by LED irradiation and enable the regulation of cellular and subcellular function based on the settings of specific LED modules. This notion of modifying cellular activity by narrow light bands is termed photomodulation. Available LED devices are arranged as panels such that large surface areas can be treated simultaneously. Light-emitting diodes that emit light in the 590-nm range yielded significant results. A specific sequence in light pulsation prompted fibroblast stimulation in cell culture.56 The mechanism of action is believed to be stimulation of the mitochondria to activate the electron transport chain and thereby up-regulate cellular production. New adenosine triphosphate formation immediately after LED exposure has been demonstrated to increase fibroblast activity.57 Fibroblast stimulation in this manner may yield more collagen and elastin and less metalloproteinase, an enzyme responsible for the degradation of collagen. This is corroborated by immunohistochemical staining of pretreatment and posttreatment biopsy specimens. Preliminary clinical work in which 47 patients underwent treatment with the LED module (Light BioScience, Virginia Beach, Va) demonstrated improvement of skin tone, texture, and rhytids by 44%.58 Another multicenter study was conducted in which 93 patients with mild to moderate photodamage received 8 LED treatments within a 4-week period. Treatments with the unit (Gentlewaves LED Photomodulation unit; Light BioScience) were administered at least 2 days apart. Fluence ranged from 0.1 to 0.8 J/cm² according to a preset sequence code. An improvement in skin texture was noted by 87% of the patients. Periocular rhytids were reduced by 56% at the 6-month follow-up. Digital microscopy of 10 patients demonstrated a 50% to 90% improvement in skin texture. There were no adverse events59 (Figure 2).

RADIOFREQUENCY

Radiofrequency energy is electromagnetic radiation energy ranging from 300 GHz to 3 kHz. Delivery of radio-
frequency energy to living tissue is thought to induce dermal heat to critical temperatures of 65°C to 75°C, causing collagen to denature and allowing wound healing with subsequent contraction. Epidermal temperatures should range between 35°C and 45°C. A device that emits 6 MHz of radiofrequency via a monopolar contact surface has been used for the improvement of mild to moderate facial laxity. A preliminary study with one system (Thermacool System; Thermage, Inc, Hayward, Calif) reported its efficacy in the treatment of nasolabial folds and jowls (Figure 3). Energy settings ranged from 106 to 144 J, and treatment areas involved the lower two thirds of the face and the lateral neck. Monthly treatments (range, 1-3) were administered. Of 24 patients, 17 had clinical improvement of their nasolabial folds and jowls at 1 to 3 months following their treatments.60 There have been additional reports of the treatment’s efficacy in the lower face and neck region.61 Periorbital tightening has also been reported with this device.62

A pilot study reported the histological and ultrastructural effects of various settings using radiofrequency treatment (Thermage, Inc) on bovine tendon and in vivo human skin.63 Bovine tendon was treated at settings ranging from 471 to 500 J and at various cryogen delivery settings. A preliminary study with one system (Thermacool System; Thermage, Inc, Hayward, Calif) reported its efficacy in the treatment of nasolabial folds and jowls (Figure 3). Energy settings ranged from 106 to 144 J, and treatment areas involved the lower two thirds of the face and the lateral neck. Monthly treatments (range, 1-3) were administered. Of 24 patients, 17 had clinical improvement of their nasolabial folds and jowls at 1 to 3 months following their treatments.60 There have been additional reports of the treatment’s efficacy in the lower face and neck region.61 Periorbital tightening has also been reported with this device.62

A pilot study reported the histological and ultrastructural effects of various settings using radiofrequency treatment (Thermage, Inc) on bovine tendon and in vivo human skin.63 Bovine tendon was treated at settings ranging from 471 to 500 J and at various cryogen delivery settings. After treatment, biopsy specimens were processed for transmission electron microscopy. Abdominal skin from 2 women undergoing abdominoplasty was treated with the radiofrequency device before excision. Each subject had 8 treatment areas. In the first subject, 4 of the 8 areas were treated with 95 J using a 1-cm² treatment tip. Energy was delivered for 2.1 seconds, and cryogen cooling consisted of 23 milliseconds during 1 second of precooling, 33 milliseconds during 2.1 seconds of on-time cooling, and 33 milliseconds during 3 seconds of postcooling. Biopsy specimens were obtained before treatment, within 4 minutes of treatment, and 8 weeks after treatment for light and electron microscopic examination.

Ultrastructural analysis of bovine tendon demonstrated enlarged collagen fibrils throughout the treatment area. The absence or intensity of cooling affected the depth of collagen fibril change. No cooling resulted in most collagen changes occurring in the most superficial depths (100% in the first 1 mm of tissue). Medium cooling led to deeper collagen being affected (10% at 1 mm, 30% at 1-2 mm, and 1% at 2-3 mm). High cooling resulted in 20% of fibril alteration at 2 to 3 mm, 20% at 3 to 4 mm, 10% at 4 to 5 mm, and 1% at 5 to 6 mm. Light and electron microscopic examination of human skin samples did not show any changes between the control and treatment groups. The only difference was the presence of a superficial perivascular infiltrate in the day 2 treatment group. Elastin stains demonstrated no difference. In the second subject, mild perivascular and perifollicular inflammation was seen in the skin treated with 104 and 181 J compared with control. No other changes were noted between the treated skin and control. Electron microscopy of human skin showed a loss of distinct borders of collagen fibrils and an increase in size. There was an average 9% change in collagen fibrils at 104 J, an average 8% change at 133 J, and an average 18% change at 181 J. No change was observed in the control group. On Northern blot analysis, treated skin had higher levels of collagen messenger RNA on days 2 and 7 after treatment, a 2.4- and 1.7-fold increase, respectively, compared with control skin. This is highly suggestive of increased collagen gene expression.

A series of 24 patients was treated with radiofrequency (Thermacool System) to improve the upper one third of the face. By using a 1-cm² treatment tip, treatment settings were 16 for the midforehead, 14 for the lateral forehead, and 12 for the temporal region. One pass was performed. For each patient, a pretreatment photograph was taken, as was a posttreatment photograph between 4 and 12 weeks after treatment. No adverse effects were reported. A statistically significant elevation of the eyebrow was seen in most patients at 1, 2, and 3
months after the procedure. At the 3-month follow-up, 87.5% of the patients had at least 0.5 mm or greater eyebrow elevation. However, only 36% of patients self-assessments reported improvements.64

**PLASMAKINETIC SKIN REJUVENATION**

A pilot study of a new device called PlasmaKinetic Skin Rejuvenation (Gyrus Group PLC, Brookshire, England) using radiofrequency and nitrogen gas emission has demonstrated improvement of perioral rhytids.65 A plasma composed of highly excited ionized gas is generated within a stream of nitrogen and decays in a defined manner, releasing energy. As the plasma hits tissue, energy is imparted. Energy delivery to the tissue can range from 1 to 4 J. Preliminary results suggest there may be nonablative changes in the dermis at lower energy settings and with multiple passes. Early work with this device at high energy levels suggests that a unique aspect of this technology is the more rapid wound healing and reduced erythema seen after treatment compared with postoperative healing seen with CO2 or Er resurfacing. Additional studies investigating these issues, including full-face treatments at ablative and nonablative energy levels, are ongoing.

**FRAXEL**

A new technology that has recently been described (Fraxel Skin Treatments; Reliant Technologies Inc, Palo Alto, Calif) is based on the idea of fractional photothermolysis. This innovation involves the creation of microscopic zones of thermal injury (microthermal zones [MTZs]) that are 30 to 50 µm in diameter in a gridlike fashion and, therefore, not visible to the naked eye.66 Emitting 1500 nm, the fiber laser system delivers energy to depths of 400 to 700 µm. In a pilot study, 15 subjects underwent one treatment on the inner forearm at 3 different MTZ densities (400, 1600, and 6400 per square centimeter), for a constant energy of 5 mJ. The low and middle densities were tolerated well, with resultant mild erythema resolving within 1 week. The high density was associated with persistent erythema for 3 months. Histologically, there were discrete zones of thermal injury in the epidermis and midreticular dermis seen after treatment. Reepithelialization was complete in 1 day. Increased mucin and undulating patterns of reticular ridges were noted at 3 months.67

Periorbital rhytids on unilateral sides of 30 patients were treated using the fiber laser with a handheld scanning device delivering a fixed laser pattern. The handpiece moved at 0.5 cm/s across the skin. Subjects were divided into 4 treatment groups: 1480 nm and 6 mJ per MTZ; 1550 nm and 6 mJ per MTZ; 1535 nm and 10 mJ per MTZ; and 1535 nm and 12 mJ per MTZ. Subjects received 4 treatments at 4- to 7-day intervals. One treatment consisted of 10 passes to create an MTZ density of 2500 per square centimeter. The average fluence per pass was 1.5 to 3 J/cm². At the 1-month follow-up, 12% showed mild improvement, 30% showed noticeable improvement, and 54% showed moderate to significant improvement. Moderate improvement in skin texture was seen in 53%. At 3 months, 34% of the subjects had at least moderate improvement in rhytids and 47% had at least moderate improvement in skin texture. There was also demonstrable immediate skin shrinkage, then skin relaxation at 1 month, and shrinkage again at 3 months. These changes are comparable to the shrinkage pattern seen with ablative procedures.67

Multiple treatment sessions seem to be necessary to achieve optimal results. Preliminary findings suggest superior results compared with those of nonablative therapies and rhytids improvement approaching that of laser resurfacing (Richard Fitzpatrick, MD, oral communication, August 2004). Unique aspects of this innovation are the minimal healing time and the potential application of this treatment to colored skin. Further studies are necessary to determine optimal treatment settings, to evaluate the longevity of clinical improvement, and to explore potential applications for dyschromias and the treatment of darker skin types.

**CONCLUSIONS**

Nonablative treatments do not produce the same degree of improvement as resurfacing techniques, but they are an excellent alternative for people who want aesthetic improvement with a minimal recovery period. Indeed, reported results have not always been consistent and speculations about their clinical efficacy have been raised.68,69 However, there is abundant evidence demonstrating clinical effectiveness, substantiated by objective measurements and histological analysis.70 A fair cross comparison of the multiple studies and devices is difficult given the disparate methods, treatment settings, and outcome measures that are reported. Thus far, no single nonablative device has emerged as the most superior system. The decision to choose one system over another may be based on the particular concerns of the patient.71 A patient who wants concomitant improvement in redness, texture, and tone may benefit from the PDL. Individuals with mild dyschromia may be well suited for treatment with the Q-switched Nd:YAG laser. Those who want a reduced pore size and reduced oil production are good candidates for the 1450-nm diode laser or the 1320-nm Nd:YAG laser system. Future studies may elucidate predictive factors in determining which patients will benefit maximally and reliably from nonablative therapies.

Nonablative rejuvenation has great applicability in the treatment of darker skin types, making it an attractive option for individuals with atrophic scars or those who want to improve their skin texture and tone but are not candidates for skin resurfacing procedures because of the increased risk of pigmentary alterations. The ease and tolerability of the treatments, the lack of downtime, and the low risk of epidermal injury and complications make nonablative treatments a mainstay therapeutic modality for all skin types. It is anticipated that continued further advancements in light-based technology will provide greater aesthetic enhancement and more impressive changes.

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REFERENCES


Announcement

The Association of Medical Illustrators recently recognized an illustration published in the ARCHIVES. In the article by Fernando Pedroza, MD, titled “A 20-Year Review of the ‘New Domes’ Technique for Refining the Drooping Nasal Tip” (2002;4:157-163), Figure 6 received a Certificate of Merit award. The illustration was displayed at the Cleveland Clinic (Cleveland, Ohio) during the Association of Medical Illustrators 59th Annual Meeting (July 28-August 1, 2004). The artist, Cassio Lynm, MA, CMI, is the recipient of the certificate; he worked in conjunction with Dr Pedroza and Wayne Larrabee, Jr, MD, to create the figure. Mr Lynm is a medical illustrator for JAMA.