JAMA Dermatology | Review

Laser Treatment of Nongenital Verrucae
A Systematic Review

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IMPORTANCE Although cutaneous warts are common lesions, full remission is not always achieved with conventional therapies. Laser modalities including carbon dioxide (CO_2), erbium:yttrium-aluminum-garnet (Er:YAG), pulsed dye (PDL), and Nd:YAG have been investigated as alternative treatments for warts.

OBJECTIVE To review the use and efficacy of lasers for treating nongenital cutaneous warts.

EVIDENCE REVIEW Published randomized clinical trials (RCTs), cohort studies, case series, and case reports involving laser treatment of nongenital warts were retrieved by searching PubMed with no date limits. Quality ratings of studies were based on a modified version of the Oxford Centre for Evidence-Based Medicine scheme for rating individual studies. A higher emphasis was placed on RCTs and prospective cohort studies with large sample sizes and detailed methodology.

FINDINGS There were 35 studies published between 1989 and 2015 that comprised an aggregate of 2149 patients. Simple and recalcitrant nongenital warts treated with lasers show variable response rates (CO_2 laser, 50%-100%; Er:YAG laser, 72%-100%; PDL, 47%-100%; and Nd:YAG laser, 46%-100%). Current RCTs suggest that PDL is equivalent to conventional therapies such as cryotherapy and cantharidin. Combination therapies with lasers and other agents including bleomycin, salicylic acid, and light-emitting diode have shown some success.

CONCLUSIONS AND RELEVANCE Lasers can be an effective treatment option for both simple and recalcitrant warts. The lasers most studied for this purpose are CO_2, PDL, and Nd:YAG, and of these, PDL has the fewest adverse effects. Currently, use of lasers for wart treatment is limited by lack of established treatment guidelines. Future studies are needed to compare laser modalities with each other and with nonlaser treatment options, and to establish optimal treatment protocols.

JAMA Dermatol. 2016;152(9):1025-1033. doi:10.1001/jamadermatol.2016.0826
Published online April 27, 2016. Corrected on July 20, 2016.

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Cutaneous warts are benign neoplasms caused by human papillomavirus (HPV) infection of keratinocytes. Warts are commonly diagnosed lesions, with an estimated 10% incidence.[1] Common warts, which can arise on any part of the body, account for 70%, while plantar and flat warts account for 24% and 3.5%, respectively. The remaining 2.5% includes anogenital warts and mucous membrane warts (eg, oral, laryngeal).[2]

Despite high prevalence, warts can pose a therapeutic challenge. No monotherapy has achieved complete remission in every case. The most common treatments are salicylic acid (SA) and cryotherapy. Other modalities include chemical agents (eg, cantharidin, formaldehyde), chemotherapeutics (eg, podofilox, fluorouracil, bleomycin sulfate), contact sensitizing agents (eg, dinitrochlorobenzene, squaric acid dibutyl ester), and immunomodulators (eg, interferon, imiquimod). Surgical excision, curettage, and laser therapy are physical means of treating warts.[2]

Various laser modalities have been explored for wart treatment, including carbon dioxide (CO_2), erbium:yttrium-aluminum-garnet (Er:YAG), pulsed dye (PDL), and Nd:YAG lasers. We reviewed the literature on the use and efficacy of laser modalities for the treatment of nongenital cutaneous warts.

Methods

A PubMed search for randomized clinical trials (RCTs), cohort studies, case series, and case reports involving laser treatment of nongenital warts was conducted using the keywords "laser," "wart," and/or "verruca" with no date limits. Exclusion criteria included studies pertaining to anogenital warts and review articles. The quality rating scheme was modified from the Oxford Centre for Evidence-Based Medicine for ratings of individual studies: (1) properly powered and conducted randomized clinical trial; systematic review with

meta-analysis; (2) well-designed controlled trial without randomization; prospective comparative cohort trial; (3) case-control studies; retrospective cohort study; (4) case series with or without intervention; cross-sectional study; (5) opinion of respected authorities; case reports.

Results

The PubMed search yielded 173 articles, of which 35 (5 RCTs, 25 cohort studies, 3 case series, 2 case reports) studies published between 1989 and 2015 remained after exclusion criteria were applied, comprising an aggregate of 2149 patients.

Carbon Dioxide Lasers

The CO_2 laser was the initial laser modality used to treat warts and has been used since the 1980s.[3-5] It functions by emitting infrared light at 10 600 nm, a wavelength absorbed by water. The CO_2 laser treats warts via 2 mechanisms. First, when the beam is focused it can be used as a scalpel to excise the wart in a hemostatic manner. Second, when the beam is defocused, it vaporizes layers of HPV-infected epidermis.[6-8]

No RCTs comparing the use of CO_2 laser with other modalities in treating nongenital warts have been published. Cohort studies report that simple and recalcitrant common, palmar, plantar, periungual, and subungual warts have been successfully treated with CO_2 laser, with response rates ranging from 50% to 100% (**Table 1**).[4,6,9-16] Investigators have used the focused mode with spot sizes ranging from 0.2 to 1.0 mm and power ranging from 8 to 25 W. The defocused mode has generally been used with a spot size of 2 mm with power ranging from 3 to 25 W. Many studies used both settings, using the focused mode for excision and the defocused mode for vaporization and hemostasis. The number of laser passes used depended on the depth of the lesion, but studies reported using 2 to 4 passes per wart. In most cases, 1 or 2 treatment sessions were needed to achieve remission.[9-12]

Studies have investigated the use of CO_2 laser for treating periungual and subungual warts, which are lesions generally difficult to treat with cryotherapy.[10,11] Lim and Goh[10] conducted the largest study and treated periungual and subungual warts in 40 patients with CO_2 laser (spot size, approximately 2 mm; defocused; 3-15 W). The CO_2 laser clearance rate for warts for which prior conventional treatment had failed was 48% whereas lesions treated with CO_2 laser as first-line treatment had an 80% clearance rate ($P = .04$). Thus, it may be reasonable to use CO_2 lasers as first-line therapy for periungual and subungual warts.[10] However, potential adverse effects include permanent nail matrix damage, scarring, and nail changes such as distal onycholysis and thickening.[10,11,14]

Combination treatment involving CO_2 laser and other modalities has also been investigated. A cohort study by Mitsuishi et al[15] included 31 patients and demonstrated that excision with CO_2 laser (spot size, 0.2 mm; 8-10 W) followed by artificial dermis application achieved an 89% clearance rate for plantar warts after 1 treatment session. Three months after treatment, HPV DNA was undetectable at the postoperative site. Recurrence occurred in 11% of patients, but minor recurrences were effectively treated with SA. Finally, a case report of a single patient treated with 2 CO_2 laser treatments (spot size, 0.2-0.4 mm; 1-3 W) spaced 1 month apart, followed by 2 weeks of imiquimod, 5%, application effectively treated recalcitrant warts on the external ear.[16]

Unfortunately, treatment of warts with the CO_2 laser can be complicated by substantial adverse effects include scarring, hypopigmentation, postoperative pain, and prolonged wound healing.[6,8] Scarring has been reported in up to 61% of patients treated for recalcitrant warts and appeared unrelated to wart duration or location.[6] Immunosuppressed patients are especially susceptible to scarring and delayed wound healing.[17] Some suggest that superpulsed CO_2 lasers may minimalize thermal damage, decreasing complications.[6,18] Nevertheless, other lasers such as PDL have been used for wart treatment because of the substantial adverse effects associated with CO_2 laser therapy.[19]

Key Points

Question What is the efficacy of lasers in nongenital wart treatment?

Findings In this systematic review, simple and recalcitrant nongenital warts treated with carbon dioxide, erbium:yttrium-aluminum-garnet (Er:YAG), pulsed dye, or Nd:YAG lasers showed clearance rates ranging from 47% to 100%. Randomized clinical trials (RCTs) suggest that pulsed dye laser therapy is equivalent to conventional therapies such as cryotherapy and cantharidin in treating simple nongenital warts; however, RCTs comparing laser modalities with each other and with conventional therapies are generally limited.

Meaning Current research shows that lasers can effectively treat warts, but future research is necessary to establish treatment guidelines and to determine optimal laser parameters.

Er:YAG Lasers

The Er:YAG laser emits a wavelength of 2940 nm, which is more than 10 times more selective for water compared with the 10 600-nm CO_2 laser. Therefore, the Er:YAG laser vaporizes tissue while minimizing thermal damage.[20] Its mechanism in treating warts is through direct ablation of the lesion's epidermis, layer by layer, until normal tissue is visualized.[21]

Several cohort studies have evaluated the use of the Er:YAG laser in treating warts (**Table 2**).[21-24] The first study, by Drnovšek-Olup and Vedlin,[21] evaluated 6 patients with nonrecalcitrant flat warts and achieved 100% clearance after 1 session (spot size, 3-5 mm; pulse duration, 0.2-0.4 ms; 4-5 J/cm^2; 2-10 Hz; 3-5 pulses). Follow-up at a mean of 8 months showed no recurrence.[21] A second study by Wollina et al[22] involved 69 patients with recalcitrant periungual and plantar warts and achieved 72% complete response after 1 treatment (spot size, 3 mm; 5.7-11.3 J/cm^2; 8-15 Hz). Plantar warts were more resistant than periungual warts (14% vs 6% no response). Unfortunately, there was a high relapse rate (24%), especially for plantar warts, at 3-month follow-up. Following this study, Wollina[23] explored the efficacy of the Er:YAG laser followed by topical podofilox, 0.5%, in 35 patients with palmoplantar warts. One Er:YAG treatment (spot size, 3 mm; 5.7-11.3 J/cm^2; 8-15 Hz) was administered and after wound healing (1 week later), topical podofilox was applied for 3 consecutive days, followed by a 4-day break period. The podofilox regimen was repeated for 4 to 6 cycles. A complete response was shown by 89% of patients, with 6% relapse after 3 months.

Table 1. Summary and Comparison of Studies Using the Carbon Dioxide (CO_2) Laser to Treat Warts

Source	Study Design; Treatment	Quality Rating[a]	Power, W	Spot Size, Focus, No. of Pulses	Patients, No.	Wart Site/ Type	Remission Rate, Patients, %	Follow-up, mo
Mancuso et al,[4] 1991	Retrospective survey; CO_2 laser	4	10-15	1 mm, focused for circumscribing, then defocused for vaporization	166	Plantar	75[b]	3-72
Logan and Zachary,[6] 1989	Nonblinded, nonrandomized, prospective; CO_2 laser	2	8-20	Defocused, mean of 4 pulses per wart	18	Plantar, hands; recalcitrant	56	10
Sloan et al,[9] 1998	Retrospective survey; CO_2 laser	4	10-22	Defocused	92	Common; recalcitrant	64	12
Lim and Goh,[10] 1992	Nonblinded, nonrandomized, retrospective; CO_2 laser	3	3-15	2 mm, defocused	40	Periungual, subungual	57 (80 for first line, 48 for recalcitrant)	10
Street and Roenigk,[11] 1990	Nonblinded, nonrandomized, retrospective; CO_2 laser	3	10-20 W initially, then 3-7 W with next pass	2 mm, defocused	17	Periungual; recalcitrant	71	12
Oni and Mahaffey,[12] 2011	Retrospective case note review and survey; CO_2 laser	4	8-25	1 mm focused, then defocused for hemostasis	22	Plantar, hands, body; recalcitrant	96	71.5
Serour and Somekh,[13] 2003	Nonblinded, nonrandomized, prospective; CO_2 laser	2	5 Superpulsed	1 mm focused, then 2 mm defocused	40	Fingers, plantar, hands, knees, legs, arms, elbow; recalcitrant	100	12
Lauchli et al,[14] 2003	Nonblinded, nonrandomized, prospective; CO_2 laser	2	3-10 Superpulsed	2-4 Pulses per wart	22	Hands, plantar, neck, trunk, arms, toes; recalcitrant	50	3
Mitsuishi et al,[15] 2010	Nonblinded, nonrandomized, prospective; CO_2 laser + artificial dermis	2	8-10 Superpulsed	0.2 mm, focused, pulse duration 300-400 μs	31	Plantar	89[b]	3-12
Zeng et al,[16] 2014	Case report; CO_2 laser + imiquimod cream,5%	5	1-3	0.2-0.4 mm	1	Ear; recalcitrant	100	12

[a] Quality rating scheme is modified from the Oxford Centre for Evidence-Based Medicine for ratings of individual studies: (1) properly powered and conducted randomized clinical trial; systematic review with meta-analysis; (2) well-designed controlled trial without randomization; prospective comparative cohort trial; (3) case-control studies; retrospective cohort study; (4) case series with or without intervention; cross-sectional study; (5) opinion of respected authorities; case reports.

[b] Wart clearance rate.

Thus, compared with Er:YAG alone, Er:YAG and podofilox achieved a higher response and lower recurrence rate after 3 months.

Trelles et al[24] investigated combination treatment with Er:YAG ablation (spot size, 2 mm; pulse duration, 350 μs; 96 J/cm^2; 8 Hz) immediately followed by red light-emitting diode (LED) therapy (wavelength, 633 nm; 20 minutes; 96 J/cm^2) to treat plantar warts. Notably, higher fluence settings (96 J/cm^2) were used compared with previous studies. Red LED light was used because of its antiviral properties and its ability to accelerate wound healing. Fifty-eight patients were treated with 1 Er:YAG laser treatment immediately followed by LED, which was repeated 2, 6, and 10 days after laser treatment. Patients were able to ambulate without pain on the same day the first session was performed and completely healed by day 15. All lesions cleared with treatment and there was low recurrence (6%) after 12 months.

Adverse effects of Er:YAG laser therapy include discomfort during treatment, especially for plantar warts, and persistent redness (up to 3 weeks).[21,22] Wart treatment with the Er:YAG laser is generally well tolerated, and pigment changes, wound infections, and scarring were not observed in these particular studies.[25-29] Time to epithelialization of treated lesions varied between 7 and 10 days.[21-23]

Pulsed Dye Lasers

Pulsed dye lasers emit a wavelength from 585 to 595 nm, consistent with a hemoglobin absorption peak. It is hypothesized that PDL destroys the characteristically dilated superficial capillaries that supply warts, thereby starving the epidermal cells that host viral molecules.[1,30,31] Furthermore, it has been suggested that PDL destroys the HPV virus itself as a result of the virus's heat-sensitive properties.[1,32-34]

Pulsed dye laser therapy has been used to treat simple and recalcitrant common, palmar, plantar, and flat warts, with studies reporting remission rates ranging from 47% to 100% (Table 3).[1,30,33-48] Differences in laser protocols may account for variable responses. Pulsed dye laser parameters varied among studies, including spot size (5-10 mm), pulse duration (38 ns to 1.5 ms), fluence (5-15 J/cm^2), cooling methods, and number of pulses (range, 1-5). The mean number of treatments ranged from 1.3 to 6.3, and treatment intervals ranged from 1 to 8 weeks. Most warts were pared down prior to PDL to remove hyperkeratotic skin and improve light penetration. Palmar warts may have higher response rates than plantar warts (Ross et al[39]: 75% palmar vs 20% plantar; Sethuraman et al[40]: 93% palmar vs 69% plantar). Pulsed dye lasers can treat warts in cosmetically

Table 2. Summary and Comparison of Studies Using Erbium:Yttrium-Aluminum-Garnet (Er:YAG) Laser Therapy to Treat Warts

Source	Study Design; Treatment	Quality Rating[a]	Er:YAG Parameters	No. of Patients (No. of Warts)	Wart Site/Type	Resolution Rate, Warts, %
Drnovšek-Olup and Vedlin,[21] 1997	Nonblinded, nonrandomized, prospective; Er:YAG	2	Spot size: 3-5 mm Pulse duration: 0.2-0.4 ms Fluence: 4-5 J/cm^2 Frequency: 2-10 Hz Pulses: 3-5	6 (8)	Flat; simple	100
Wollina et al,[22] 2001	Nonblinded, nonrandomized, prospective; Er:YAG	2	Spot size: 3 mm Fluence: 5.7-11.3 J/cm^2 Frequency: 8-15 Hz	69 (NR)	Periungual and plantar; recalcitrant	72[b]
Wollina,[23] 2003	Nonblinded, nonrandomized, prospective; Er:YAG + topical podofilox, 0.5%	2	Spot size: 3 mm Fluence: 5.7-11.3 J/cm^2 Frequency: 8-15 Hz	35 (NR)	Palmoplantar	89[b]
Trelles et al,[24] 2006	Nonblinded, nonrandomized, retrospective; Er:YAG + LED	2	Spot size: 2 mm Pulse duration: 350 μs Fluence: 96 J/cm^2 Frequency: 8 Hz LED parameters: wavelength 633 nm, 20 min, 96 J/cm^2	58 (141)	Plantar	100

Abbreviations: LED, light-emitting diode; NR, not reported.

[a] Quality rating scheme is modified from the Oxford Centre for Evidence-Based Medicine for ratings of individual studies: (1) properly powered and conducted randomized clinical trial; systematic review with meta-analysis; (2) well-designed controlled trial without randomization; prospective comparative cohort trial; (3) case-control studies; retrospective cohort study; (4) case series with or without intervention; cross-sectional study; (5) opinion of respected authorities; case reports.

[b] Patient clearance rate.

sensitive areas such as the face with eradication rates ranging from 41% to 100%.[33,34,43]

The results of 2 large studies suggest that higher fluence settings may lead to higher remission rates. First, the 120-patient cohort study of Park and Choi[38] reported a clearance of 49.5% for simple and recalcitrant flat, periungual, plantar, and common warts using PDL (spot size, 5 mm; 7-10 J/cm^2; no cooling; 2 pulses). Significantly higher clearance was reported at higher fluence settings (9.5 J/cm^2). Second, a retrospective analysis by Sparreboom et al[45] of 208 patients with recalcitrant common and plantar warts showed 86% remission with PDL (spot size, 7 mm; pulse duration, 1.5 ms; 12.5-15 J/cm^2; no cooling; 1-5 pulses). The investigators suggested that high efficacy was achieved because of more aggressive fluence settings than previously described. Higher success was also associated with increased number of treatment sessions (up to 6) at 3- to 4-week intervals.

Whereas the number of RCTs comparing PDL with other treatment modalities is limited, 3 recent RCTs suggest that PDL is not superior to conventional therapies. First, Robson et al[1] demonstrated no difference in clearance rate of common and plantar warts when comparing PDL (spot size, 5 mm; 9.0-9.5 J/cm^2; no cooling; 2 pulses) with conventional therapies such as cryotherapy and cantharidin (PDL 66% vs conventional 70%). The other 2 RCTs showed a nonsignificantly better response with PDL. Passeron et al[35] showed no difference in patients cleared of palmoplantar warts with PDL (spot size, 5 mm; pulse duration, 0.45 ms; 9 J/cm^2; cooling via cryogen spray; 5 pulses) and cryotherapy vs cryotherapy alone (31.5% vs 18.8%, P = .46). Furthermore, Akhyani et al[36] reported that PDL (spot size, 7 mm; pulse duration, 1.5 ms; 15 J/cm^2; no cooling; 2 pulses) was not statistically superior to cryotherapy in treating common warts (51% vs 38%; P = .23) despite using a high fluence. Collectively, these results suggest that PDL is not more efficacious than conventional therapies in treating common, palmar, and plantar warts, but offers another option. However, it is notable that many of the warts treated in these RCTs were nonrecalcitrant, and there may be a better response to PDL with recalcitrant warts. For example, the cohort study of Kenton-Smith and Tan[33] treated warts on the hands, feet, face, and extremities with PDL (spot size, 5-7 mm; pulse duration, 450 μs; 6-9 J/cm^2; cooling by means of aloe vera gel; 3 pulses) and showed significantly higher clearance of recalcitrant warts compared with simple warts (92% vs 75%; P = .02). Similarly, Jacobsen et al[41] observed higher clearance of recalcitrant warts compared with previously untreated warts (68% vs 47%; P = .02) using a fluence of 8 J/cm^2.

Several authors have combined PDL with other modalities. Specifically, 2 groups recently treated recalcitrant warts with PDL immediately followed by intralesional bleomycin. First, Pollock and Sheehan-Dare[47] achieved 89% remission in recalcitrant hand warts using PDL (spot size, 7 mm; 10 J/cm^2; no cooling; 3-4 pulses) followed by bleomycin (0.5 IU/mL; median, 0.3 mL/wart) after a mean of 1.8 treatment sessions. Notably, there was a high response in a subset of immunocompromised patients (80%). Second, Dobson and Harland[48] used PDL (spot size, 7 mm; pulse duration, 1.5 ms; 12-15 J/cm^2; no cooling; 3 pulses) followed by intralesional bleomycin (1 mg/mL; <1000 IU/wart) to treat recalcitrant palmoplantar warts, achieving 60% remission rate with a mean of 2 cycles. Higher response (92%) was noted with increased number of treatment sessions and with local anesthetic use to allow for more aggressive treatment.

Salicylic acid has also been used in combination with PDL. Akarsu et al[37] compared treatment with 30% SA twice a day for 5 days prior to PDL (spot size, 5 mm; pulse duration, 350 μs; 6-9 J/cm^2; cooling by means of ice pack; 3 pulses) with treatment with PDL alone. After 5 sessions, overall resolution rates were similar between SA and PDL vs PDL alone (70% vs 67%). However, among the warts that completely cleared, the mean number of treatment sessions needed for resolution was lower in the SA and PDL group compared with the PDL alone group (2.2 vs 3.1 sessions).

Adverse effects of PDL therapy include local pain during and after the procedure, bullae, crusting, scarring, and temporary

Table 3. Summary and Comparison of Studies Using Pulsed Dye Laser (PDL) or Nd:YAG Laser Therapy to Treat Warts

Source	Study Design; Treatment	Quality Rating[a]	Laser Parameters	Treatment Intervals (Mean No. of Treatments)	No. of Patients (No. of Warts)	Wart Site/ Type	Resolution Rate, Warts, %
Robson et al,[1] 2000	RCT, single blinded, prospective; cryotherapy and/or cantharidin vs PDL	1	PDL: 585 nm Spot size: 5 mm Fluence: 9.0-9.5 J/cm^2 Cooling: none Pulses: 2	4 wk (2.06 and/or cantharidin, 2.00 PDL)	35 (194)	Common, plantar	66 vs 70[b]
Passeron et al,[35] 2007	RCT, single-blinded, prospective; cryotherapy vs cryotherapy + PDL	1	PDL: 595 nm Spot size: 5 mm Pulse duration: 0.45 ms Fluence: 9 J/cm^2 Cooling: cryogen spray Pulses: 5	3 wk (≤3 sessions)	35 (105)	Palmoplantar	31.5 vs 18.7[b]
Akhyani et al,[36] 2010	RCT, single-blinded, prospective; cryotherapy vs PDL	1	PDL: 585 nm Spot size: 7 mm Pulse duration: 1.5 ms Fluence: 15 J/cm^2 Cooling: none Pulses: 2	3 wk (≤4 sessions)	39 (82)	Common	51 vs 38[b]
Akarsu et al,[37] 2006	RCT, single-blinded, prospective; PDL vs salicylic acid, 30% + PDL	1	PDL: 585 nm Spot size: 5 mm Pulse duration: 350 μs Fluence: 6-9 J/cm^2 Cooling: ice pack Pulses: 3	4 wk (3.1, 2.2 SA + PDL)	19 (66)	Hand, leg, chin, chest	70 vs 67[b]
Schellhaas et al,[30] 2008	Nonblinded, nonrandomized, prospective; PDL	2	PDL: 583-587 nm Spot size: 5 mm Pulse duration: 450 μs Fluence: 8-12 J/cm^2 Cooling: none Pulses: 3-5	2 wk (3.3, 3.8 feet)	73 (366)	Hands, feet; recalcitrant	89.0
Kenton-Smith and Tan,[33] 1999	Nonblinded, nonrandomized, prospective; PDL	2	PDL: 585 nm Spot size: 5 or 7 mm Pulse duration: 450 μs Fluence: 6-9 J/cm^2 Cooling: aloe vera gel Pulses: 3	6-8 wk (2.1, 1.6 simple)	28 (123)	Face, hands, foot, arms and legs	92 recalcitrant, 75 simple; P = .02
Vargas et al,[34] 2002	Nonblinded, nonrandomized, prospective; PDL	2	PDL: 585 nm Spot size: 5 mm Fluence: 9-13 J/cm^2 Cooling: none Pulses: 1-2	3-4 wk (1.3)	12 (NR)	Face	100
Park and Choi,[38] 2008	Nonblinded, nonrandomized, prospective; PDL	2	PDL: 585 nm Spot size: 5 mm Pulse duration: 38 ns Fluence: 7-10 J/cm^2 Cooling: none Pulses: 2	2-3 wk (2.8)	120 (372)	Flat, periungual, plantar, common	49.5
Ross et al,[39] 1999	Nonblinded, nonrandomized, prospective; PDL	2	PDL: 585 nm Spot size: 5-10 mm Pulse duration: 450 μs Fluence: 5-10 J/cm^2; mean, 9.4 J/cm^2 Cooling: none Pulses: 1-5	2-4 wk (3.4)	33 (96); 30 patients with recalcitrant warts	Plantar, digital, periungual and subungual, body	48[c]
Sethuraman et al,[40] 2010	Retrospective survey; PDL	4	PDL: 585 nm Spot size: 5-7 mm Fluence: 6.5-9.5 J/cm^2 Cooling: none Pulses: 3	2.5-4 wk (3.1)	61 (NR)	Perineal, perianal, face, palmar, plantar; recalcitrant	75[c]
Jacobsen et a1,[41] 1997	Nonblinded, nonrandomized, prospective; PDL	2	PDL: 585 nm Fluence: 8 J/cm^2	1-2 mo (1.72)	32 (NR)	Common; recalcitrant and simple	68 recalcitrant, 47.1 simple; P = .02
Jain and Storwick,[42] 1997	Nonblinded, nonrandomized, prospective; PDL	2	PDL: 585 nm Spot size: 5.0 mm Pulse duration: 450 μs Fluence: 8.1-8.4 J/cm^2 Cooling: none Pulses: 3-5	1-4 wk (2.6)	33 (97)	Plantar	70
Grillo et al,[43] 2014	Nonblinded, nonrandomized, prospective; PDL	2	PDL: 595 nm Spot size: 5 or 7 mm Pulse duration: 500 μs Fluence: 9 J/cm^2 Cooling: continuous airflow Pulses: 1-3	3 wk (1.75)	32 (382)	Facial flat	78

(continued)

Table 3. Summary and Comparison of Studies Using Pulsed Dye Laser (PDL) or Nd:YAG Laser Therapy to Treat Warts (continued)

Source	Study Design; Treatment	Quality Rating[a]	Laser Parameters	Treatment Intervals (Mean No. of Treatments)	No. of Patients (No. of Warts)	Wart Site/ Type	Resolution Rate, Warts, %
Park et al,[44] 2007	Nonblinded, nonrandomized, prospective; PDL	2	PDL: 585 nm Spot size: 5 mm Fluence: 7-10 J/cm^2 Cooling: none Pulses: 2	2-3 wk (3.1)	56 (206)	Common, periungual, plantar, flat	48.1
Sparreboom et al,[45] 2014	Retrospective case series; PDL	4	PDL: 595 nm Spot size: 7 mm Pulse duration: 1.5 ms Fluence: 12.5-15 J/cm^2 Cooling: none Pulses: 1-5	1-4 wk (6.3)	208 (718)	Common, plantar; recalcitrant	86
Kopera,[46] 2003	Nonblinded, nonrandomized, prospective; flashlamp-pumped PDL	2	PDL: 585 nm Spot size: 7 mm Pulse duration: 450 μs Fluence: 8 J/cm^2 Cooling: none	2-6 wk (3.38)	126 (NR)	Common, hands, feet; simple and recalcitrant	62.7[c]
Pollock and Sheehan-Dare,[47] 2002	Nonblinded, nonrandomized, prospective; PDL + intralesional bleomycin (0.5 IU/mL)	2	PDL: 585 nm Spot size: 7 mm Fluence: 10 J/cm^2 Cooling: none Pulses: 3-4	4 wk (1.8)	10 (18)	Hand; recalcitrant	89
Dobson and Harlan,[48] 2014	Retrospective case series; PDL + intralesional bleomycin (1 mg/mL normal saline)	2	PDL: 595 nm Spot size: 7 mm Pulse duration: 1.5 ms Fluence: 12-15 J/cm^2 Cooling: none Pulses: 3	3 mo (2)	22 (NR)	Hand, foot; recalcitrant	60[c]
El-Mohamady et al,[49] 2014	RCT; Nd:YAG vs PDL	1	Nd:YAG Spot size: 7 mm Pulse duration: 20 ms Fluence: 100 J/cm^2 Cooling: none (PDL: spot size, 7 mm; pulse duration, 0.5 ms; fluence, 8 J/cm^2; cooling, none)	2 wk (4.65:YAG, 5.05 PDL)	46 (NR)	Plantar; recalcitrant	Nd:YAG, 78[c]; PDL, 74[c]
Han et al,[26] 2009	Case series; Long-pulsed Nd:YAG	4	Nd:YAG Spot size: 5 mm Pulse duration: 20 ms Fluence: 200 J/cm^2 Cooling: none Pulses: 1-2	4 wk (1.49)	348 (348)	Common, palmoplantar, periungual; simple and recalcitrant	96
Kimura et al,[25] 2014	Nonblinded, nonrandomized, prospective; Long-pulsed Nd:YAG	2	Nd:YAG Spot size: 5 mm Pulse duration: 15 ms Fluence: 150-185 J/cm^2 Cooling: ice pack	4 wk (3.8)	20 (34)	Periungual, subungual, plantar, fingers, toes; recalcitrant	56
Bingol et al,[29] 2015	Nonblinded, nonrandomized, prospective; Long-pulsed Nd:YAG	2	Nd:YAG Spot size: 3 mm Pulse duration: 23 ms Fluence: 180-200 J/cm^2 Cooling: cold air device Pulses: 3	12 mo	51 (146)	Hand; recalcitrant	88.4 with 1 session, 100 with 2 sessions
Goldberg et al[19] 2015	Nonblinded, nonrandomized, prospective; Low-energy (200 mJ) long-pulsed Nd:YAG	2	Nd:YAG Pulse duration: 1 ms 5.5 W Cooling: none Pulses: 4-8	1 mo	25 (63)	Hand	46[c]
Pfau et al,[28] 1994	Case report; Nd:YAG	5	Nd:YAG Spot size: 8 mm Pulse duration: 20 s 10 W Cooling: none Pulses: 1	6 wk	1 (2)	Finger and plantar; recalcitrant	100

Abbreviations: NR, not reported; RCT, randomized clinical trial.

[a] Quality rating scheme is modified from the Oxford Centre for Evidence-Based Medicine for ratings of individual studies: (1) properly powered and conducted randomized clinical trial; systematic review with meta-analysis; (2) well-designed controlled trial without randomization; prospective comparative cohort trial; (3) case-control studies; retrospective cohort study; (4) case series with or without intervention; cross-sectional study; (5) opinion of respected authorities; case reports.

[b] Intervention vs control.

[c] Patient clearance rate.

Table 4. Summary of Recommendations for Laser Treatment of Nongenital Warts

Recommendation	Grade of Recommendation[a]	Quality of Evidence[a]	Source
Proper safety precautions including gloves, smoke evacuation, and face masks should be used during laser treatment of warts	1	A	Garden et al,[53] 1988; Hallmo and Naess,[57] 1991; Gloster and Roenigk,[55] 1995; Garden et al,[54] 2002
CO_2, PDL, and Nd:YAG are the laser modalities most studied for the treatment of nongenital warts and have been shown to be effective for this purpose	2A	B	Logan and Zachary,[6] 1989; Street and Roenigk,[11] 1990; Lim and Goh,[10] 1992; Jacobsen et al,[41] 1997; Jain and Storwick,[42] 1997; Sloan et al,[9] 1998; Kenton-Smith and Tan,[33] 1999; Ross et al,[39] 1999; Robson et al,[1] 2000; Vargas et al,[34] 2002; Kopera,[46] 2003; Lauchli et al,[14] 2003; Serour and Somekh,[13] 2003; Akarsu et al,[37] 2006; Passeron et al,[35] 2007; Park and Choi,[38] 2008; Schellhaas et al,[30] 2008; Han et al,[26] 2009; Akhyani et al,[36] 2010; Oni and Mahaffey,[12] 2011; Kimura et al,[25] 2014; El-Mohamady et al,[49] 2014; Grillo et al,[43] 2014; Bingol et al,[29] 2015; Goldberg et al,[19] 2015
PDL has a favorable adverse effect profile compared with the Nd:YAG or CO_2 laser for the treatment of nongenital warts	2A	B	Logan and Zachary,[6] 1989; Street and Roenigk,[11] 1990; Lim and Goh,[10] 1992; Sloan et al,[9] 1998; Ross et al,[39] 1999; Ozleur et al,[17] 2001; Lauchli et al,[14] 2003; Akarsu et al,[37] 2006; Park and Cho,[38] 2008; Schellhaas et al,[30] 2008; Han et al,[26] 2009; Sethuraman et al,[40] 2010; Akhyani et al,[36] 2010; Oni and Mahaffey,[12] 2011; El-Mohamady et al,[49] 2014; Grillo et al,[43] 2014; Kimura et al,[25] 2014; Goldberg et al,[19] 2015

Abbreviations: CO_2, carbon dioxide; PDL, pulsed dye.

[a] According to criteria by Robinson et al[58]: Grade of recommendation: 1, strong recommendation; high-quality, patient-oriented evidence; 2A, weak recommendation; limited-quality, patient-oriented evidence; 2B, weak recommendation; low-quality evidence. Quality of evidence: A, systematic review/meta-analysis; randomized clinical trials with consistent findings; all-or-none observational studies; B, systematic review/meta-analysis of lower-quality clinical trials or studies with limitations and inconsistent findings; lower-quality clinical trial; cohort study; case-control study; C, consensus guidelines, usual practice, expert opinion, case series.

pigment changes.[30,31,38] Although multiple treatment sessions are generally necessary for remission, PDL has significantly fewer adverse effects than the CO_2 laser.[36] Compared with cryotherapy, PDL has a lower incidence of pain and bulla formation.[36] Overall, the current literature supports that PDL is a safe and effective option for wart treatment, although cure rates do not appear to be higher than for other treatment options.[38,39]

Nd:YAG Lasers

The postulated mechanism by which the Nd:YAG laser treats warts is similar to that of PDL. The Nd:YAG laser emits a wavelength of 1064 nm and targets hemoglobin's modest absorption peak between 800 and 1100 nm, causing coagulation and destruction of warts' dermal blood vessels. Compared with PDL, the Nd:YAG laser's longer wavelength and lower hemoglobin and melanin absorption coefficients permit for deeper penetration of light energy into the hyperkeratotic epidermis that is characteristic of warts.[25,26,50] Microscopic examination of lesions after Nd:YAG laser treatment show separation of the dermoepidermal junction, epidermal necrosis, and coagulated capillaries, with minimal effect on adjacent tissue.[25,26] Notably, histologic studies showed absence of HPV DNA after Nd:YAG laser treatment, compared with 96% of HPV DNA remaining after cryotherapy.[27]

Several studies have evaluated the use of the Nd:YAG laser in the treatment of simple and recalcitrant common, palmoplantar, periungual, and subungual warts, with efficacies ranging from 46% to 100% (Table 3).[19,25,26,28,29,49] Laser protocol varied among studies, with the following ranges: spot size (3-7 mm), pulse duration (1-20 ms), fluence (100-200 J/cm^2), cooling methods, number of pulses (1-8), treatment intervals (2 weeks to 12 months), and mean number of treatments (1.49-4.65). The largest study to date evaluating the use of Nd:YAG in treating warts was conducted by Han et al.[26] This study involved 348 patients treated for simple and recalcitrant common, palmoplantar, and periungual warts with Nd:YAG (spot size, 5 mm; pulse duration, 20 ms; 200 J/cm^2; no cooling; 1-2 pulses). The wart clearance rate was 96% after a mean of 1.49 treatments. There were differences in clearance rates after initial treatment depending on location (72.6% for common warts vs 44.1% for palmoplantar warts). Furthermore, 2 recent studies investigated the efficacy of Nd:YAG lasers in treating dorsal and palmar hand warts.[19,29] The first study, by Goldberg et al,[19] used low-energy (200 mJ) Nd:YAG and included 25 patients, showing 46% clearance after up to 3 treatments (pulse duration, 1 ms; 5.5 W; no cooling; 4-8 pulses). All lesions showed at least partial response, defined as at least 50% reduction in wart size. The second study, by Bingol et al,[29] included 51 patients with recalcitrant hand warts and reported higher clearance rates, with 88.4% of warts clearing with 1 treatment session, and 100% clearance after 2 sessions (spot size, 3 mm; pulse duration, 23 ms; 180-200 J/cm^2; cooling via cold air device; 3 pulses). A high clearance rate was achieved using an overlapped triple circle pulse technique in which the wart was aligned at the intersection of the circles of 3 laser pulses. A smaller study by Kimura et al[25] evaluated 20 patients with recalcitrant hand, foot, periungual, and subungual warts and found 56% complete clearance and 80% partial clearance after a mean of 3.8 treatment sessions (spot size, 5 mm; pulse duration, 15 ms; 150-185 J/cm^2; cooling by means of ice pack >10 pulses).

A recent RCT by El-Mohamady et al[49] compared the efficacy of Nd:YAG (spot size, 7 mm; pulse duration, 20 ms; 100 J/cm^2; no cooling; 1 pulse) and PDL (spot size, 7 mm; pulse duration, 0.5 ms; 8 J/cm^2; no cooling; 1 pulse) in treating recalcitrant plantar warts in 46 patients. Although clearance rates were not significantly different between the 2 groups (Nd:YAG 78% vs PDL 74%), Nd:YAG was associated with more complications, including hematoma (28%), secondary bacterial infection (10%), and severe pain. There was no statistically significant difference in relapse after either Nd:YAG or PDL treatment at 3 to 6 months' follow-up (9% vs 13%). Therefore, PDL may be a preferred treatment option due to its more manageable adverse effect profile.

Optimal laser parameters have not been established, but it is possible that shorter pulse duration and lower fluence may decrease adverse effects. Han et al[26] achieved a high success rate (96%) in treating common, periungual, and palmoplantar warts but used relatively higher settings (pulse duration, 20 ms; 200

J/cm^2), which produced adverse effects including serious pain, transient numbness, hemorrhagic bullae, pigment changes, and nail dystrophy. Although Kimura et al[25] achieved a lower success rate (56%) with less intensive settings (pulse duration, 15 ms; 150-185 J/cm^2), they cleared recalcitrant warts with no substantial adverse effects.

Other Lasers

Other laser modalities have been investigated in wart treatment. Yang et al[51] used holmium:YAG lasers (wavelength, 2140 nm; 1.2-1.5 J; 10-12 Hz; 10 W) to treat 42 patients with recalcitrant facial warts and all warts cleared after 1 session. Adverse effects were mild and included mild atrophic scarring (7%) and pigment changes (14%), which clinically improved at 6-month follow-up. Two patients experienced recurrence at 6-month follow-up. Given the tolerable adverse effect profile, Yang et al[51] concluded that holmium:YAG lasers may be an option for treating warts in cosmetically sensitive areas such as the face.

The 532-nm potassium titanyl phosphate (KTP) laser has also been explored in wart treatment. Gooptu and James[52] used KTP (spot size, 1 mm; pulse duration, 30 ms; 15-18 J/cm^2; no cooling; 2 pulses) to treat recalcitrant plantar, palmar, and periungual warts in 25 patients, with 48% responding completely. The warts were treated monthly and complete clearance was seen after a median of 3 treatments. Adverse effects included moderate discomfort during the procedure, scabbing, blistering, and bruising. Scarring and nail atrophy were not observed and recurrence only occurred in patients who stopped treatment prematurely.

Safety Precautions

It is important that patients and practitioners take proper safety precautions during laser wart treatment procedures. Intact HPV DNA particles have been shown to be present in the plume produced by the CO_2 laser during wart treatment, raising concerns for respiratory papillomatosis.[53-55] Because large amounts of plume are produced with the CO_2 laser, smoke evacuation from the surgical field with the suction tip close to the tissue is obligatory, in addition to precautions such as gloves and face masks.[53] In contrast, 1 study showed that Er:YAG plumes do not contain viable HPV fragments.[56] Plumes formed from Nd:YAG treatment of warts have not been studied in the laboratory, but there is a report of a surgeon who treated anogenital condylomas with Nd:YAG lasers and subsequently developed laryngeal papillomatosis with HPV 6 and 11.[57] Thus, in addition to using gloves and face masks, it is prudent to use a smoke evacuator in Nd:YAG treatment of warts.[57] There are currently no studies discussing the presence of HPV in PDL plumes.

Discussion

Although cutaneous warts are common, they can be therapeutically challenging. Fortunately, a growing body of evidence suggests that lasers can effectively treat nongenital warts and they should therefore be considered an additional modality in the wart treatment armamentarium. Currently, comparisons of lasers to nonlaser treatment modalities are limited, but a few studies suggest that PDL and conventional therapies such as cryotherapy and cantharidin are comparable in efficacy. We present several recommendations regarding laser treatment of warts (**Table 4**). Specifically, CO_2, PDL, and Nd:YAG are the laser modalities most studied for wart treatment, and of these PDL has the most favorable adverse effect profile. Whereas wart treatment with Er:YAG, holmium:YAG, and KTP lasers has been evaluated in smaller numbers of studies, additional trials are needed to clarify the utility of these devices. Overall, at this time, there is a lack of evidence to provide clear guidelines for selection of laser device for different warts and there is inadequate evidence to provide specific laser setting recommendations. Laser treatment of warts is, however, an additional therapeutic option and the studies reviewed here can provide a starting point in determining settings.

Conclusions

Lasers can be an effective treatment option for both simple and recalcitrant warts. The lasers most studied for this purpose are CO_2, PDL, and Nd:YAG, and of these, PDL has the fewest adverse effects. Currently, use of lasers for wart treatment is limited by lack of established treatment guidelines. Future studies are needed to compare laser modalities to each other and to nonlaser treatment options, and to establish optimal treatment protocols.

ARTICLE INFORMATION

Accepted for Publication: March 1, 2016.

Published Online: April 27, 2016. doi:10.1001/jamadermatol.2016.0826.

Author Contributions: Ms Nguyen and Dr Korta had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Korta, Chapman.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Nguyen, Korta, Chapman.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Chapman.
Administrative, technical, or material support: Nguyen.
Study supervision: Korta, Kelly.

Conflict of Interest Disclosures: None reported.

Funding/Support: The Iridex Laser was provided to the University of California Irvine Department of Dermatology as an educational grant from Iridex Corporation.

Role of the Funder/Sponsor: Iridex Corporation had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Correction: This article was corrected online July 20, 2016, for a missing author middle initial.

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NOTABLE NOTES

Dermatology and Possession

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In the classic film *The Exorcist*, Father Damien Karras is asked, "How does a doctor end up as a priest?" Though the dual vocation of doctor-priest may have fallen out of favor in modern medical practice, societies have attributed death and disease to a higher power since time immemorial. For most of human history, the medical and the mystical have been one and the same.

This holds particularly true for dermatologic conditions. Readily visible, these conditions unfortunately generate disgust and result in the social rejection of afflicted individuals.[1] The more stigmatizing the disorder, the greater the belief in a magical or religious etiology. For instance, the Ayurvedic medical system considers leprosy and vitiligo to be more serious and stigmatizing than tinea versicolor. Accordingly, while nearly half of patients with leprosy and vitiligo interviewed in 1992 attributed their disorder to supernatural causes, only 17% of patients with tinea versicolor did so.[2]

Possession was a commonly cited etiology in India and Indonesia, where the Hindu Sátkuváris air spirits were believed to cause smallpox, measles, and chickenpox by entering the bodies of unsuspecting passersby. Only by consulting a medium could the offending spirit be identified, based on the clinical manifestations of the disease; for example, the queen of the Sátkuváris was thought to both cause and cure smallpox. The appropriate intervention was then propitiation of the spirit with tributes of coconuts and fowls.[2,3]

In Nigeria, on the other hand, possession was a cure: the Yoruba believed that Sopono spirits induced carbuncles, boils, and smallpox. Therapy involved a possession ritual orchestrated by elderly women who had been previously afflicted; this technique was meant to both identify the spirit responsible and, in itself, reverse the ailment.[3]

As the corpus of medical knowledge has grown, supernatural interpretations of skin disorders have been largely discarded. There are now medical explanations available for the dermatologic manifestations of erstwhile demonic possessions. Consider *The Exorcist*: when the demon first takes up residence in Regan MacNeil's body, her skin blanches and becomes averse to holy water. When it later assumes total control, in desperation she somehow scrawls "help me" on her own skin.

Holy water aversion could easily be mistaken for polycythemia vera, in which water can induce sensations of itching, tingling, and even burning. "Skin writing" could be nothing more than a manifestation of dermographic urticaria, in which firm strokes or pressure on the skin immediately result in wheals, essentially turning the skin into a canvas. One must therefore consider which is more probable: a girl with unmet psychiatric needs and polycythemia vera comorbid with dermographic urticaria… or demonic possession? Perhaps the diagnostic benefits of a stint in the seminary deserve another look.

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