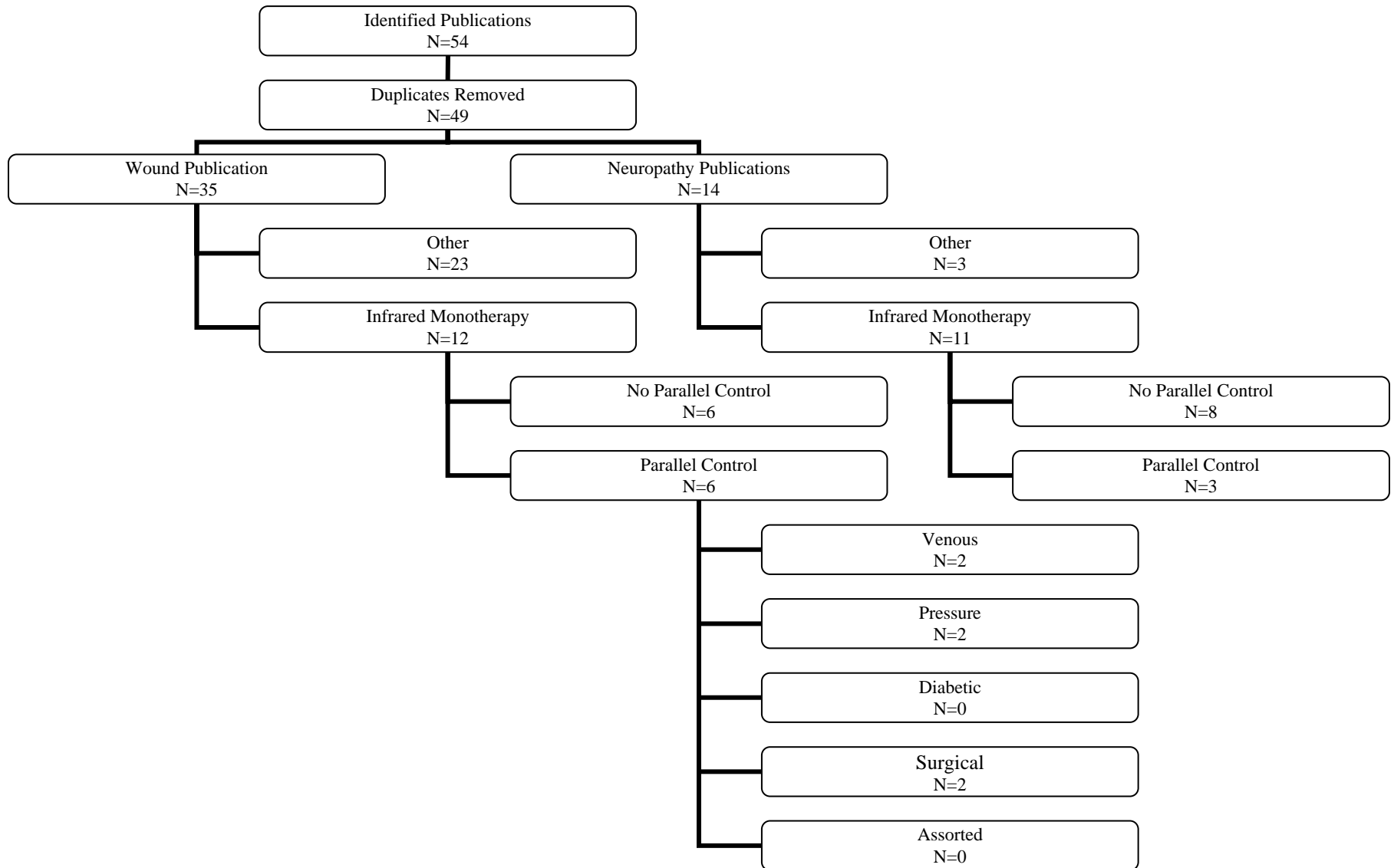


Appendix B Studies Reviewed



Appendix C

Evidence Tables

Appendix C is divided into 8 tables:

1. Venous Ulcers,
2. Pressure Ulcers,
3. Diabetic Ulcers,
4. Assorted Ulcers,
5. Surgical Wounds,
6. Peripheral Neuropathy,
7. Placebo-Controlled Studies of Infrared Monotherapy for Wound Healing, and
8. Placebo-Controlled Studies of Infrared Monotherapy for Peripheral Sensory Neuropathy

Tables 1 – 6 are each divided into 3 panels, (A, B and C) because the number of columns exceeds page width. The column headings for all the A panels are: Author, Publication Type, Publication Date, MEDLINE Availability, Country of Origin, Type of Wound or Neuropathy, Outcome Test(s), and Treatment including Light Parameters. The column headings for all the B panels are: Author, Study Type, Randomization Status, Control Type, Blinding Status, IRB Status, Consent Status, Patient Number, and Funding Source. The column headings for all the C panels are: Author, Exclusion of Other Medications (Rx) and/or Treatments (Tx), Presence of a Washout Period, Trial Duration, Duration of Actual Treatment (Tx) Regimen, Regimen for Treatment (Tx) [Length of Treatment Sessions, Frequency of Treatment Sessions, Number of Treatment Sessions, Energy Dose], Post-treatment Withdrawal Period/Evaluation, and Study Results. The individual studies are arranged in the panels by publication date in reverse chronologic order.

Tables 7 and 8 do not have separate panels.

Table 1
Venous Ulcers*

Panel A

Author	Publication Type	Publication Date	Medline	Country	Type of Wound	Test Parameter	Treatment (Device-Type-If Pulsation-Frequency)
Kopera, Kokol, Berger, Haas	3 papers for 1 study	2005	Yes 1 of 3	Austria	Venous Present 3mo-3yr, 1-8cm Failed compression Arterial disease, diabetes, renal disease, cancer & autoimmune disease excluded	Change in ulcer area by planimetry at tx end 28 days & 90 day follow-up	Laser (Hermann Heltschl) Continuous-685 nm VS LED-semi-sham tx Polychromatic red incoherent light VS Nothing
Clements, Grimes, Walsh, Allen, Baxter	Abstract	2004	No	Ireland	Venous	Pain VAS Change in ulcer area by tracing & planimetry after 4 weeks tx	Laser (Omega) ?? - Pulsed-660-950 nm
Lanzafame, Stadler, Haerum, Coleman, Rhodes, Whelan	Abstract	2003	No	USA	Diabetic Venous Stasis*	Change in ulcer size by unspecified measurement techniques Time to complete closure Durability of healing	Diode (Quantum Devices) ??-??-670 & 880 nm
Lagan, McKenna, Witherow, Johns, McDonough, Baxter	Paper	2002	Yes	Ireland	Venous Could not have received laser therapy in last 2 months	Pain VAS Change in ulcer area by photos & digitized tracing after 4 weeks tx & another 8 weeks w/o tx	Laser Diodes (Omega Biotherapy 3ML) GaAlAs-pulsed-660-950 nm
Franek, Krol, Kucharzewski	Paper	2002	No	Poland	Venous crural Arterial disease excluded	Change in ulcer area/volume by planimetry w/o fixed tx period	Laser (CTL-1106MX) GaAlAs-continuous-810 nm
Krol, Franek, Hunka-Zurawinska, Bil, Swist, Polak, Bendkowski	Paper Appears to be an earlier subgroup of that in Franek paper	2001	Yes	Poland	Venous crural Arterial disease excluded	Change in ulcer area/volume by planimetry w/o fixed tx period	Laser (CTL-1106MX) GaAlAs-continuous-810 nm
Lichtenstein, Borag	Paper	1999	No	Israel	Venous Ulcers that had not improved over 6 months	Change in wound size Percent of wound closure	Laser HeNe-??-632.8 nm (Yr 1) GaAlAs-??-830 nm (Yrs 2-4)
Gupta, Filonenko, Salansky, Sauder	Paper Also in 1993 abstract by Telfer	1998	Yes	Canada	Venous Patients with arterial disease, malignancy, immune compromise, or ulcers $\geq 12\text{cm}^2$ excluded	Change in ulcer size by unspecified measurement techniques. Rate of healing Serial photos-taken, but use not specified	(International Medical Instruments IR7 & R22) Pulsed-880 nm & Continuous-660 nm
Kleiman, Simmer, Braksmas, Morag, Lichtenstein	Paper Also in 1996 abstract by Braksmas	1996	Yes	Israel	Venous Present >6 months Patients with arterial disease, CHF, diabetes, hypercoagulation, or hematologic	% patient wound closure % recurrence rate	1 wound-Laser (Medical Electronics) GaAs-continuous-785 nm AND Multiple wounds-Laser (Medec ML 300)

					disease excluded		GaAlAs-pulsed-765 nm HeNe-pulsed-632.8 nm
Lundeberg, Malm	Paper	1991	Yes	Sweden	Venous	% patient wound closure at 12 weeks	Laser HeNe-continuous-632.8 nm
Malm, Lundeberg	Paper	1991	Yes	Sweden	Venous Arterial disease, diabetes, rheumatoid disease, trauma excluded	Change in healing by tracings. Classified as shallow or deep (>1 cm). Powered to detect 40% change.	Laser (Irradia) GaAs-pulsed-904 nm
Sugru, Carolan, Leen, Feely, Moore, Shanik	Paper	1990	Yes	Ireland	Venous Arterial disease, diabetes, collagen disease excluded	Pain VAS Transcutaneous O ₂ level Histologic fibrin & capillary density Change in area of granulation Until healed or 12 weeks	Laser (Endoclaser 465) GaAlAs-continuous-780 nm (Benson IR CEB-S) GaAs-pulsed-904 nm
Bihari, Mester	Paper	1989	No	Hungary	Crural venous	Qualitative change in ulcers & number w complete healing	Laser & Diode HeNe-??-?? nm VS HeNe-pulsed-904 nm vs Non-coherent, non-polarized light
Crous, Malherbe	Paper	1988	No	S Africa	Venous Refractory to unspecified treatment	Change in ulcer perimeter & area Qualitative changes in appearance via photo	Laser (UP Space Midlaser)
Brunner	Paper	1986	Yes	Germany	Venous	Duration of treatment Whether closure occurred	Laser Krypton-??-647 nm
Santoiani, Monfrecola, Marellotta, Ayala	Paper	1984	Yes	Italy	Venous Present 2-23 months W/o prior surgery	Change in area of epithelialization by wound tracings at 30 days	Laser HeNe-??-632.8 nm at 2 energy levels

VAS=Visual analogue pain scale ??=Parameter for light therapy not provided Tx=Treatment

Table 1
Venous Ulcers

Panel B

Author	Study Type	Randomized	Control	Blind	IRB	Consent	Patient Number	Funding Source
Kopera, Kokol, Berger, Haas	<i>Prospective</i> No indication of number rejected in screening Unspecified time period 1 drop-out during trial, 6 during follow-up	Yes	Placebo & Polychromatic red light	Tx-Blind-17 Placebo-Blind-17 Control-No Blind-10	Yes	Yes	44 patients 17 patients-laser, 17 patients-polychromatic red light, 10 patients -control 1 site	NI
Clements, Grimes, Walsh, Allen, Baxter	<i>Prospective</i> Unspecified time period	NI	Placebo	Independent wound assessment	Yes	NI	8 patients 4 patients tx; 4 patients control 1 site	NI
Lanzafame, Stadler, Haerum, Coleman, Rhodes, Whelan	<i>Prospective</i> No indication of number rejected in screening. Unspecified time period	Yes	Placebo	Sham dosing (same wavelengths, but at 5% of exposure that experimental group received Investigators broke blind of ongoing study for abstract	NI	NI	6 patients 4 treatment, 2 sham ? # sites	NI
Lagan, McKenna, Witherow, Johns, McDonough, Baxter	<i>Prospective</i> No indication of number rejected in screening Unspecified time period	Yes	Placebo Self-during withdrawal	Physiotherapist not blinded. Investigators & patients blinded.	Yes	Yes	15 patients, 16 wounds 8 patients-tx, 7 patients-control 1 site	Vice Chancellor Scholarship
Franek, Krol, Kucharzewski	<i>Prospective</i> No indication of number rejected in screening Unspecified time period	Yes	Placebo & Sham device	Tx-Blind-21 Placebo-Blind-22 Control-No Blind-22	Yes	NI	65 patients 21 patients-laser, 22 patients-sham, 22 patients-control 1 site	NI
Krol, Franek, Hunka-Zurawinska, Bil, Swist, Polak, Bendkowski	<i>Prospective</i> No indication of number rejected in screening Unspecified time period	Yes	Placebo & Sham device	Tx-Blind-17 Placebo-Blind-15 Control-No Blind-17	Yes	NI	49 patients 17 patients-laser, 15 patients-sham, 17 patients-control 1 site	NI
Lichtenstein, Borag	<i>Prospective</i> No indication of number rejected in screening 4 year period	No	Self	No	NI	NI	HeNe 42 patients GaAIs 20 patients 1 site	NI
Gupta, Filonenko, Salansky, Sauder	<i>Prospective</i> No indication of number rejected in screening Unspecified time period	Yes	Sham device	Double-blind (Sham device)	NI	Yes	12 wounds 9 patients ?? patients-tx, ?? patients-sham ? # sites	NI

	1 drop-out not included in analysis							
Kleiman, Simmer, Braksma, Morag, Lichtenstein	<i>Retrospective observation</i> No indication of number rejected in screening. Data collection 1967-95	No	Self	No	NI	NI	29 patients-1 wound 13 patients- ≥ 2 wounds 1 site	NI
Lundeberg, Malm	<i>Prospective</i> No indication of number rejected in screening. Unspecified time period. 12 withdrawals.	Yes	Placebo	Coded tracings assessed by computer	NI	NI	46 patients 23 patients in each group 1 site	Tore Nilsons Foundation
Malm, Lundeberg	<i>Prospective</i> No indication of number rejected in screening. Unspecified time period 10 withdrawals.	Yes	Placebo	Double-blind Sham device	NI	NI	42 patients 21 patients in each group 1 site 10 withdrawn after randomization	Karolinska Institutet Foundation, King Gustav Fund, Torsten&Ragnar Soderbergs Foundation, Lars Hiertas Fund
Sugru, Carolan, Leen, Feely, Moore, Shanik	<i>Prospective</i> No indication of number rejected in screening. Unspecified time period	NI	Self prior to 1 of 2 laser tx. Self w biopsy elsewhere.	NI	NI	NI	12 patients 4 patients 780 nm laser 8 patients 904 nm laser 1 site	Lasers provided by Benson Laser & Catmar Ltd
Bihari, Mester	<i>Prospective</i> No indication of number rejected in screening. Unspecified time period	Yes	Red light & 2 IR tx groups	Double-blind	NI	NI	45 patients 15 in each group 1 site	Laser provided by Lasotronic
Crous, Malherbe	<i>Prospective</i> No indication of number rejected in screening. July-August 1987	Yes	No $\frac{1}{2}$ patients (n=3) tx w UV	NI	NI	NI	6 patients 3 patients-laser, 3 patients-UV 1 site	Trial use of device from maker, Glynamics
Bruner	<i>Prospective</i> No indication of number rejected in screening. Unspecified time period	NI	No	NI	NI	NI	24 patients	NI
Santoianni, Monfrecola, Marellotta, Ayala	<i>Prospective</i> No indication of number rejected in screening. Unspecified time period	Yes Modified	If ulcer 5+ cm, $\frac{1}{2}$ treated n=10 If >1 ulcer, 1 treated	Single-blind	NI	NI	61 patients 16-low energy density-1J/cm ² 17-high energy density-4J/cm ² 28 patients-control 1 site	Italian National Research Council

IRB=Institutional Ethics Review Board NI=Not indicated UV=Ultraviolet light

Table 1
Venous Ulcers

Panel C

Author	Exclusion of Other Rx/Tx	Washout	Trial Duration	Regimen: Tx Duration	Regimen: Tx Frequency and Dose	Post-Tx Withdrawal Period/Evaluation	Results
Kopera, Kokol, Berger, Haas	Control=Hydrofiber dressing & compression	No	90 days	28 days	4J/cm ² for 6-18 min daily x14 days, then QOD x14 days	Yes/ 62 day follow-up 6 drop-outs	No difference
Clements, Grimes, Walsh, Allen, Baxter	Control=Conservative nursing care	No	11 weeks	4 weeks	4J/cm ² 2 days/week x4 weeks	Yes 7 week follow-up	No difference for healing. Unclear if changes in pain were statistically significant
Lanzafame, Stadler, Haerum, Coleman, Rhodes, Whelan	Control=usual care	No	≤60 treatments ≤15 weeks	≤60 treatments ≤15 weeks	4J/cm ² /wavelength/tx 4x/week x ≤15 weeks OR 50 mW/cm ² x1.7 min/wavelength	No	Treatment could end because of skin grafting Reported a trend to greater extent of closure (p=0.058)
Lagan, McKenna, Witherow, Johns, McDonough, Baxter	Control=water cleansing & dressing or compression	No	12 weeks	4 weeks	12J/cm ² 1 day/week x4 weeks	Yes 8 week follow-up	No difference
Franek, Krol, Kucharzewski	Control=Potassium permanganate wash, topical pharmaceuticals, compression dressing	No	~5 weeks	~5 weeks	4J/cm ² . Time based on ulcer size 5 days/week for ~5 weeks	No	No difference
Krol, Franek, Hunka-Zurawinska, Bil, Swist, Polak, Bendkowski	Control=Potassium permanganate wash, topical pharmaceuticals, & compression therapy	No	~5 weeks	~5 weeks	4J/cm ²	No	No difference
Lichtenstein, Borag	Unspecified	No	~2-14 weeks+ variable follow-up	~2-14 weeks	Tx QOD	Variable 6 mo to 6 yrs	Reported complete wound closure for 53 patients & closure >50% for 4 patients. Results not stratified by tx. No statistical analysis performed.
Gupta, Filonenko, Salansky, Sauder	Ulcers cleaned with saline & dressed dry Unclear # protocol violations	No	10 weeks	10 weeks	4J/cm ² each light tx 660 nm x180 sec & 880 nm x30 sec	No	Reportedly ulcer size was less with tx. Reportedly the rate of healing approached statistical significance (p=0.055). Imbalance at baseline. Duration of

							ulcers > for light tx group. Total area of ulcers used. The area & tx given to patients w multiple ulcers not provided. The response of patients w multiple ulcers not provided. Intent-to-treat analyses not conducted. Impact of protocol violations not provided. 1 patient in light tx group treated for Staph infection.
Kleiman, Simmer, Brakmsma, Morag, Lichtenstein	Prior rx continued	No	1-9 months	1-9 months	1 wound-20 min qOD Multiple wounds-15 min qOD	3-32 months (Only 35 available for follow-up)	Reportedly 36/42 had wound closure. No controls. 6 discontinuations; 2 for failure. 2 of 35 in follow-up had wound breakdown.
Lundeberg, Malm	Control=Saline wash; paste & support bandages	No	12 weeks unless earlier healing	12 weeks unless earlier healing	4 J/cm ² 2x/ week x≤12 weeks	No	No difference.
Malm, Lundeberg	Conservative tx w saline washes & compression	No	12 weeks unless earlier healing	12 weeks unless earlier healing	1.96J/cm ² . 10 minutes/tx. 2x/ week x≤12 weeks	No	No difference.
Sugru, Carolan, Leen, Feely, Moore, Shank	Prior conservative therapy continued	No	12 weeks or until healed	12 weeks or until healed	780 nm laser-15 sec/cm ² 904 nm laser-4 minutes 3x week	No	Improvement in wound healing & pain over baseline. Treatments not compared to one another. Transcutaneous O ₂ levels, capillary density, & pericapillary fibrin did not improve over baseline.
Bihari, Mester	Compression banadages & antibiotics used	No	9 months	9 months	4J/cm ² 1x week x9 months	No	Claims improvement in both treatment groups. No statistics done.
Crous, Malherbe	Dressings not standardized.	No	4 weeks	4 weeks	10 minutes 3x/week x4 weeks	No	Reported improvement. No statistical data.
Brunner	None	No	Unspecified	Unspecified	4.5J/cm ² 90 sec 2x week	No	Only 10 had complete closure & healing took longer than the 15 weeks reported in Russian literature
Santoianni, Monfrecola, Marellotta, Ayala	Control=Antiseptic compression dressing	No	Unspecified. Measurements taken at 30 days	At least 1 month	1J/cm ² or 4J/cm ² 6 days/week-at least 1 month	No	No difference

Rx=Medications Tx=Treatment J=Joules ??=Parameter for light therapy not provided

**Table 2
Pressure Ulcers**

Panel A

Author	Publication Type	Publication Date	Medline	Country	Type of Wound	Test Parameter	Treatment (Device-Type-If Pulsation-Frequency)
Taly, Nair, Murali, John	Paper	2004	Yes	India	Pressure ulcer in spinal cord injury patients Exclusion of ulcers w features limiting laser tx, w osteomyelitis, or requiring surgery	Change in Pressure Sore Status Tool Change in photographed ulcer stage	Laser-Diodes GaAlAs-??-820nm w diodes of 660, 870, 880, 940, 950 nm
Lucas, van Gemert, de Haan	Paper	2003	Yes	Holland	Pressure ulcer grade III w/o overlying eschar Patients w poorly controlled diabetes, terminal disease, & ulcer >1 yr	Absolute size & change in area by photos & tracing as well as Norton score & progression to stage IV after 6 weeks	Laser (Combilaser C501) GaAs-pulsed-904 nm
Schubert	Paper	2001	Yes	Sweden	Pressure ulcer stage II or III after fall related trauma Diabetes & CVA not excluded Malnourished/low BMI patients excluded	Ulcer size w tracing & digital planimetry Rate constant, healing rate, & survival analysis	Diodes (Biolight) Pulsed-956 & 637 in sequence
Lucas, Coenen, de Haan	Paper	2000	No	Holland	Pressure ulcer grade III w/o overlying eschar & ≤30cm ² Patients w poorly controlled diabetes, terminal disease, & ulcer >1 yr excluded	Absolute size & change in area by photos & tracing as well as Norton score after 6 weeks	Cluster laser w12 diodes (Combilaser C501) GaAl-pulsed-904 nm
Nussbaum, Biemann, Mustard	Paper	1994	Yes	Canada	Pressure ulcer in spinal cord injury patients	Rate of change in size by digitized tracing and & rate of change in depth	Laser-Diodes (Intelect 800) Pulsed-820 nm plus 660, 880, 950 nm
Lievens, Delforge	Paper	1992	Yes	Belgium	Pressure ulcer in elderly. No exclusions for concomitant dx	Diameter & depth of ulcer. Qualitative scale for necrosis & epithelialization	Laser-Diode Pulsed-904 nm

CVA=Stroke BMI=Body mass index ??=Parameter for light therapy not provided

Table 2
Pressure Ulcers

Panel B

Author	Study Type	Randomized	Control	Blind	IRB	Consent	Patient Number	Funding Source
Taly, Nair, Murali, John	<i>Prospective</i> 129 admissions, 40 w ulcers, 35 eligible for entry Unspecified time period	Yes	Placebo	Double-blind	Yes	Yes	64 wounds 35 patients tx; 29 patients control 1 site	National Institute of Mental Health & Neurosciences for data analysis. No financial ties to device maker
Lucas, van Gemert, de Haan (2003)	<i>Prospective</i> 105 eligible. 19 declined randomization. Unspecified time period	Yes	Placebo	Investigators blinded	Yes	Yes	86 patients 39 patients tx; 47 patients control 3 nursing homes	NI
Schubert	<i>Prospective</i> No indication of number rejected in screening Unspecified time period	Yes	Placebo	NI	Yes	Yes	74 randomized (37 each group) (later 2 in tx group excluded for protocol violations) 1 site	Device maker Biolight, Karolinska Institute, Gun & Bertil Stohne Fdn
Lucas, Coenen, de Haan (2000)	<i>Prospective</i> 20 enrolled. 16 randomized. Unspecified time period	Yes	Placebo	Investigators blinded	Yes	Yes	16 patients (8 each group) 4 nursing homes	Funding Health care Charities
Nussbaum, Biemann, Mustard	<i>Prospective</i> 20 randomized 4 discontinuations Unspecified time period	Yes	Placebo 2 tx groups (US/UV-ultrasound-ultraviolet & laser)	NI	NI	Yes	22 wounds 20 patients (6 patients laser; 5 patients US/UV; 9 patients control) 1 site	NI
Lievens, Delforge	<i>Prospective</i> No indication of number rejected in screening Recruitment: 1-2/1991	No	Self Monitored 1 month of routine care prior to experimental phase	NI	NI	NI	10 patients 1 nursing home tx site	NI

IRB=Institutional Ethics Review Board NI=Not indicated US=Ultrasound UV=Ultraviolet Tx=Treatment

**Table 2
Pressure Ulcers**

Panel C

Author	Exclusion of Other Rx/Tx	Washout	Trial Duration	Regimen: Tx Duration	Regimen: Tx Frequency and Dose	Post-Tx Withdrawal Period/Evaluation	Results
Taly, Nair, Murali, John	Pressure relief, saline dressings used	No	4.5 weeks or until healed	4.5 weeks or until healed	4.5J/cm ² 3 days/week for a maximum of 14 tx	No	No difference
Lucas, van Gemert, de Haan (2003)	NPUAP guidelines used	No	6 weeks	6 weeks	1J/cm ² x 125 sec 5 days/week x 6 weeks	No	No difference
Schubert	Pressure relief, saline wet-to-dry dressings, cadexomer iodine gel if local infection were used	No	10 weeks or until healed	10 weeks or until healed	9 minutes/tx Week 1-5x Week 2-4x Week 3-2x Week 4 & beyond-1x	No	Reported improvement in experimental group at 9 weeks (no information for 10) for healing rate & survival analysis, but there were high drop-out rates or protocol exclusion rates (6/37 in control; 10/37 in tx). Intent-to-treat analyses were not performed.
Lucas, Coenen, de Haan (2000)	Standard tx=frequent movement & moist dressings	No	6 weeks	6 weeks	1J/cm ² x 125 sec 5 days/week x up to 6 weeks	No	No difference
Nussbaum, Biemann, Mustard	Frequent movement, Hygeol, jemolet dressings used	No	Until healed	Until healed	4J/cm ² in 35 sec 3 days/week	No	US-UV tx better than standard or laser tx
Lievens, Delforge	Unspecified conventional tx used	1 month baseline data	1 month each of baseline, tx, & withdrawal data	1 month	10 minutes/tx Daily tx x 1 month	1 month	Reported statistically significant improvement in ulcer diameter, necrosis, epithelialization, & eschar formation after 1 month treatment & 1 month post treatment when compared to baseline. No improvement for ulcer depth. Statistical data & methods not presented.

Rx=Medications Tx=Treatment US=Ultrasound UV=Ultraviolet J=Joules

Table 3
Diabetic Ulcers*

Panel A

Author	Publication Type	Publication Date	Medline	Country	Type of Wound	Test Parameter	Treatment (Device-Type-If Pulsation-Frequency)
Powell, Carnegie, Burke (2004)	Paper (May be subset of 2006 paper)	2004	Yes	USA	Presumed diabetic wounds associated with presumed peripheral diabetic neuropathy (unspecified type diabetes) based on patient self-report Excluded patients <65 yrs, w skin ulcer, if did not improve w infrared tx	Questionnaire (no information on validation of survey) Development of new wounds	Anodyne Therapy
Landau, Schattner	Paper	2001	Yes	Israel	Diabetic ulcers that failed \geq 14 weeks of aggressive conventional therapy All had neuropathy	Complete closure of ulcer with overlying skin or scar formation	Laser (Unilaser Scan 60) HeNe/infrared-??-632.8 & 904 nm
Landau	Paper	1998	Yes	Israel	Diabetic ulcers that failed routine therapy ABI calculated, but reason for exclusion	Not specified	Laser (Unilaser Scan 60) HeNe/infrared-??-632.8 & 904 nm
Kleinman, Simmer, Brakmsa	Abstract	1996	No	Israel	Diabetic ulcers that failed conservative tx. Osteomyelitis & renal disease not excluded.	Degree of healing over an unspecified time period	Laser-2 types over time GaAs-continuous-785 nm OR (Medi-Electronics ML300) GaAs-pulsed-785 nm plus HeNe-pulsed-632.8 nm (31 w topical hyperbaric O ₂)
Lagan, Baxter, Ashford	Abstract	1996	No	Ireland	Presumably ischemic/neuropathic ulcers	Change in ulcer area by photos, tracing & planimetry after 4 weeks tx	Diode Pulsed--660-950 nm

??=Parameter for light therapy not provided ABI=Ankle brachial indices Rx=Medications Tx=Treatment US=Ultrasound UV=Ultraviolet J=Joules

*See Table 1 (Venous Ulcers) for Lanzafame et al. (Diabetic Venous Stasis Ulcers).

**Table 3
Diabetic Ulcers**

Panel B

Author	Study Type	Randomized	Control	Blind	IRB	Consent	Patient Number	Funding Source
Powell, Carnegie, Burke (2004)	<i>Cross-sectional survey & Retrospective record review</i> Insurance records from 2 unspecified DME suppliers reviewed for lists of patients treated 1/02-5/02 Patients called $\geq 3x$	No	Self Historical	Records deidentified records at some point	NI	Some authorization for med record release.	119 considered eligible 68 responded post $\geq 3x$ phone calls (51 treating doctors)	Anodyne provided funding Author Burke is the Anodyne Director of Research & Clinical Affairs
Landau, Schattner	<i>Prospective</i> First 100 patients w/o gangrene & refractory to aggressive conventional tx. 14 lost to follow-up. (233 achieved healing w/o experimental tx.) Unspecified time period	No	Self (11 patients given topical hyperbaric O ₂ alone)	No	NI	NI	100 patients 1 site	NI
Landau	<i>Prospective</i> No indication of number rejected in screening. Recruitment: 5/1995-5/1996	No Based on logistical considerations	Topical hyperbaric O ₂	NI	Yes	NI	50 patients 35 tx group; 15 control (O ₂)	NI
Kleinman, Simmer, Brakmsma	<i>Case series</i> 1989-1995	No	1 of 2 types of laser tx. Some also hyperbaric O ₂ .	NI	NI	NI	44 patients 37 NIDDM 7 IDDM	NI
Lagan, Baxter, Ashford	<i>Prospective</i> Unspecified time period	No	Self	No	Yes	NI	4 patients 1 site	NI

IRB=Institutional Ethics Review Board NI=Not indicated O₂=Oxygen Tx=Treatment

Table 3
Diabetic Ulcers

Panel C

Author	Exclusion of Other Rx/Tx	Washout	Trial Duration	Regimen: Tx Duration	Regimen: Tx Frequency and Dose	Post-Tx Withdrawal Period/Evaluation	Results
Powell, Carnegie, Burke (2004)	No	No	Unspecified Questioned 10-15 months post neuropathy improvement	Unspecified	Unspecified	Could still be using device	Reported decreased post treatment wound prevalence. Did not report on other survey questions. Reported 1 burn when patient fell asleep. Survey complicated by selection bias of those determined to be eligible as well as only 57% response rate. Performed erroneous calculations to a historic control.
Landau, Schattner	Antibiotics not stopped Glucose control used No compression, Regra- nex, recombinant skin	No	Variable	Variable	4J/cm ² in 20 minutes 2-3x week x? duration	Variable period of follow-up	Reports improvement over conventional tx, but no clear endpoints & did not compare relative roles of light & O ₂ therapy. Unclear whether patients from 1998 paper were included in this series.
Landau	Control=topical hyperbaric O ₂ . Antibiotics not stopped	No	Variable	Variable	4J/cm ² in 20 minutes 2-3x week x? duration	No	No comparative data of time to healing presented. Reported more rapid onset of pain reduction and edema reduction, but no data presented. Reportedly all healing failures occurred in patients with arterial disease.
Kleinman, Simmer, Braksmma	1 of 2 laser tx. Some also received hyperbaric O ₂ .	No	Unspecified	Unspecified	GaAs-785 nm—30 minutes GaAs-785+HeNe-632.8 nm-15 minutes Otherwise unspecified	Unspecified. Recurrence 4/44 & in adjacent site 5/44. 16/20 with complete healing had no recurrence.	Complete healing achieved in 20/44. Partial healing achieved in 11/44. Failed healing in 11/44. 2 dropped out. Data per treatment group were not provided.
Lagan, Baxter, Ashford	Conservative nursing care provided	No	4 weeks	4 weeks	4J/cm ² 7 days/week x4 weeks	No	Improvement over baseline, but no control.

Rx=Medications Tx=Treatment O₂=Oxygen J=Joules

**Table 4
Assorted Ulcers**

Panel A

Author	Publication Type	Publication Date	Medline	Country	Type of Wound	Test Parameter	Treatment (Device-Type-If Pulsation-Frequency)
Kubota	Paper	2004	Yes	Japan	Mixed Refractory to other tx. Diabetic 2, post-op 1, trauma 1, unknown 1	Not specified	Laser Diode (Luketron MDL-1005) GaAlAs-continuous defocused-830 nm
Kawalec JS, Reyes C, Penfield VK, Hetherington VJ, Hays D, Feliciano F, et al.	Paper	2001	No	USA	Mixed Diabetic 12, neurotrophic 3, venous 2, traumatic 2 Excluded ulcers with active infection or exposure of underlying structures	Change in area by direct measurement Change in appearance by photo Change in bacterial count	Laser Diode (Ceralas D15) GaAlAs-??- 980 nm
Schindl M, Keschan K, Schindl A, Schon H, Henizl H, Schindl L.	Paper	1999	Yes	Austria	Mixed Diabetic 8, radiation 5, ischemic 4, autoimmune 3 Excluded venous insufficiency grade II	Number of tx & duration of tx until closure Methods used to determine size not stated	Laser HeNe-??-632.8 nm
Horwitz, Burke, Carnegie	Paper	1999	Yes	USA	Mixed Refractory to other tx Diabetes-related 2, sclerodermal 1, venous 2	Change in wound size after digitizing photographs Observations not done on a scheduled basis.	Diodes GaAlAs-??-890 nm
Shuttleworth, Banfield	Paper	1997	Yes	UK	Mixed Treatment-mixed 2, pressure 1, venous 3 Control-ischemic-1, mixed 1, pressure 1, venous 5	Change in ulcer size by wound grids Change in Waterlow score	Laser 46 cluster probe-otherwise unspecified
Gogia, Marquez	Paper	1992	Yes	USA	Mixed-stage III Treatment-venous 2, diabetic 2, pressure 1, ischemic 1 Control-venous 1, diabetic 2, pressure 3, ischemic 0 At least 8 weeks old Excluded CVD patients	Change in ulcer area by digitized tracing after 4 weeks tx Change in ulcer depth	Laser (Omni International) HeNe-continuous-632.8 nm

??=Parameter for light therapy not provided CVD=Cardiovascular Disease

Table 4
Assorted Ulcers

Panel B

Author	Study Type	Randomized	Control	Blind	IRB	Consent	Patient Number	Funding Source
Kubota	<i>Case Series</i> Unspecified time period	No	NA	NI	NI	NI	5 patients 1 site	NI
Kawalec JS, Reyes C, Penfield VK, Hetherington VJ, Hays D, Feliciano F, et al.	<i>Prospective</i> No indication of number in screening Unspecified time period	No	Self	NI	Yes	NI	16 patients 19 ulcers From 2 sites	NI
Schindl M, Keschan K, Schindl A, Schon H, Henzl H, Schindl L.	<i>Prospective</i> No indication of number rejected in screening Recruited from 7/1996-6/1997	No	Self Other types of ulcers	NI	NI	Yes	20 patients 1 site	NI
Horwitz, Burke, Carnegie	<i>Prospective</i> No indication of number rejected in screening Recruited ~1995-1998	No (Initially randomization planned)	Self (Initially planned as controlled trial)	NI (Initially double-blind trial planned)	Yes	NI	5 patients 2 sites (Given device for home tx)	Device provided by Anodyne
Shuttleworth, Banfield	<i>Prospective</i> No indication of number rejected in screening Unspecified time period	Yes	Placebo	NI	NI	NI	14 patients (1 dropped from analysis) 6 patients-tx; 8 patients-control 1 site	NI Laser provided by unknown entity
Gogia, Marquez	<i>Prospective</i> No indication of how many rejected in screening Unspecified time period	No. Assigned to control if referral was for whirlpool	Placebo	NI	Yes	Yes	12 patients 6 patients in each group 1 site	NI

IRB=Institutional Ethics Review Board NI=Not indicated Tx=Treatment

Table 4
Assorted Ulcers

Panel C

Author	Exclusion of Other Rx/Tx	Washout	Trial Duration	Regimen: Tx Duration	Regimen: Tx Frequency and Dose	Post-Tx Withdrawal Period/Evaluation	Results
Kubota	Conventional care used.	Uncertain if all prior tx, e.g. hyperbaric O ₂ , discontinued	Variable	Variable	6.3-21J/cm ² 3-10 minutes 2x week for 3 patients 1x week for 2 patients	Monitored for recurrence. None for at least 6 months	5 healed lesions & no recurrence. No control.
Kawalec, Reyes, Penfield, Hetherington, Hays, Feliciano, et al.	NI	No	Variable	Variable	At initial visit & at least 3 visits every 2-3 weeks	No	The rate of healing did not differ by ulcer type (diabetic vs non-diabetic). The decrease in the wound bacterial count from baseline was not statistically different.
Schindl M, Keschan K, Schindl A, Schon H, Henizl H, Schindl L.	Antibiotics continued Saline washes& dry dressings used	No	Until healed	Until healed	30J/cm ² 3x week until healed	No	Diabetic ulcers healed more slowly than radiation induced ulcers. Larger ulcers required a longer period of treatment than smaller ulcers.
Horwitz, Burke, Carnegie	Prior use of conventional tx including alginate, Unna boot, collagen gel, sulfadiazine, wet-to-moist dressing, compression	Most of prior tx discontinued. Wet-to-moist dressing±compression continued	Variable	Variable	43.2 J/cm ² in 30 minutes 1x/day (patients using device at home w/o direct supervision)	3 patients w/o recurrence for ≥1 yr	Wound closure for 5 patients Results reportedly obvious to providers that patients from controlled trial switched to active devices
Shuttleworth, Banfield	Conventional dressings used	No	15 weeks	15 weeks	2x/week x15 weeks Week 1-2 minutes Week 2-3 minutes Week 4-4 minutes	No	There was imbalance at baseline with a lower Waterlow score in the control group. The reduction in wound size was 9.7% for laser patients & 63% for control patients.
Gogia, Marquez	Control=Betadine whirlpool & wet-to-dry dressing	No	4 weeks	4 weeks	2J/cm ² 5 days/week x4 weeks	No	No difference

Rx=Medications Tx=Treatment NI=Not indicated O₂=Oxygen J=Joules

Table 5
Surgical Wounds

Panel A

Author	Publication Type	Publication Date	Medline	Country	Type of Wound	Test Parameters	Treatment (Device-Type-If Pulsation-Frequency)
Lagan, Clements, McDonough, Baxter	Paper	2001	Yes	Ireland	Post operative (minor procedures) Excluded infected wounds.	Change in wound size by digital planimetry & photographic digitizing. Mean of 3 tracings at each setting used. Change in wound appearance by standardized report & photos VAS for pain	Diode Laser (CBM Master 3) GaAlAs-continuous-830 nm
Iusim, Kimchy, Pillar, Mendes	Paper	1992	Yes	Israel	Part 2-Post-operative Red light-amputations for arterial disease and/or diabetes 6, fracture 1 Infrared light-amputations for diabetes 3, diabetes+pressure ulcer 1, skin disorder 1, unspecified 1 Placebo-amputations for diabetes and/or arterial disease 6, fracture+CHF 1, Hip arthroplasty for fracture 1	Change in wound appearance by photo. Change in wound size by unspecified methods	Narrow band light (Biobeam) ??-Continuous/pulsed-940 nm ??-Continuous/pulsed-660 nm
Palmgren, Dahlin J, Beck H, Colov HC	Abstract	1991	No	Denmark	Infected post-operative abdominal wounds	Change in wound size by planimetry.	Laser Diode GaAlAs-??-820 nm

??=Parameter for light therapy not provided CHF=Congestive heart failure VAS=Visual analogue pain scale

Table 5
Surgical Wounds

Panel B

Author	Study Type	Randomized	Control	Blind	IRB	Consent	Patient Number	Funding Source
Lagan, Clements, McDonough, Baxter	<i>Prospective</i> No indication of number rejected in screening Unspecified time period	Yes	Placebo	NI	Yes	Yes	12 wounds 9 patients Laser-5 patients, 7 wounds Control-4 patients, 5 wounds 1 site	NI
Iusim, Kimchy, Pillar, Mendes	<i>Prospective</i> No indication of number rejected in screening Unspecified time period	Part 1-No Part 2-Yes	Placebo 2 tx Arms	Double-blind	NI	NI	Part 1-22 patients Part 2-21 patients, 31 wounds Infrared 7, red light 7, placebo 7	Ostrowicz Foundation, Maker of device-Amcor Electronics
Palmgren, Dahlin J, Beck H, Colov HC	<i>Prospective</i> No indication of number rejected in screening Unspecified time period	Yes	Placebo Sham device	Double-blind (Sham device)	NI	NI	18 patients 9 patients each group	NI

IRB=Institutional Ethics Review Board NI=Not indicated Tx=Treatment

Table 5
Surgical Wounds

Panel C

Author	Exclusion of Other Rx/Tx	Washout	Trial Duration	Regimen: Tx Duration	Regimen: Tx Frequency and Dose	Post-Tx Withdrawal Period/Evaluation	Results
Lagan, Clements, McDonough, Baxter	Control=dressing with polynoxylin	No	11 weeks	11 weeks or until healed	9J/cm ² 1day/week	No	No difference for wound closure or pain.
Iusim, Kimchy, Pillar, Mendes	Prior treatment continued	No	Variable	Variable	7 minutes continuous & then 7 minutes pulsed 1x/day	No	Area of post-op wounds treated w red light decreased 89%. Area of wounds treated w infrared light decreased 58%. Area of wounds treated w placebo decreased 41%. There was a statistically significant difference between red light & placebo, but not between infrared & placebo. The post-op wound size was smallest in the red light group. There was no correction for probable imbalance in wound size at baseline.
Palmgren, Dahlin J, Beck H, Colov HC	NI	No	Unspecified	Unspecified	1.6J/cm ² Unspecified regimen	No	Time to decrease in post-operative abdominal wound size in the treated group was 6.8 days vs 14.0 days in the placebo group. The respective daily healing rates were 2.45 cm ² vs 1.67 cm ² . No statistical calculations were provided.

Rx=Medications Tx=Treatment NI=Not indicated J=Joules

Table 6
Peripheral Neuropathy

Panel A

Author	Publication Type	Publication Date	Medline	Country	Type of Neuropathy	Test Parameters	Treatment (Device-Type-If Pulsation-Frequency)
Arnall, Nelson, Lopez, Sanz, Iversen, Sanz, Stambaugh, Arnall	Paper	2006	Yes	Spain	Presumed peripheral diabetic neuropathy (type 1 or 2 diabetes) Excluded patients with acute renal failure, anemia, & lower extremity wounds	Monofilament (Weinstein Esthesiometer) on 4 sites Vibratory sensation (Bioesthesiometer) Pedal temperature (Exergen scanner) Ankle/brachial indices	Diode (RevitaMed) GaAs-650 & pulsed 880 nm
Pappas	Paper	2006	No	USA	Unspecified peripheral neuropathy Mobility problems	Monofilament (unspecified device used on 5 sites) VAS Diabetic Neuropathy Scale 6 minute walk test	Diode (Anodyne) ??-??-890 nm
Harkless, Delellis, Carnegie, Burke	Paper	2006	Yes	USA	Mixed neuropathy. Diagnosis based on ICD9 codes 357 & 782). Presumed diabetic etiology based on ICD9 codes 250.61 & 250.62. Excluded patients tested with devices or monofilaments other than 10 gm or monofilament testing done on <10 sites.	Monofilament VAS	Diode (Anodyne) ??-Pulsed-890 nm
Powell, Carnegie, Burke (2005-6)	Paper (See 2004 wound paper)	2005-6	Yes	USA	Presumed peripheral diabetic neuropathy (type 1 or 2 diabetes) Apparent exclusion of those who did not improve w tx. Apparent exclusion of those using device <1month Excluded patients <65 yrs	Questionnaire (no information on validation of survey)	Anodyne Therapy ??-??-??
Cliff, Kasser, Newton, Bush	Paper	2005	Yes	USA	Presumed diabetic (self-reported diabetes) Excluded foot wounds	Monofilament (using calibrated series of monofilaments) at 4 plantar sites	Diode (Anodyne 120-4) GaAlAs-??-890 nm
Volker, Hassan, Hassan, Smock, Connor, McFee, Ferguson, Burke	Paper	2005	No	USA	Mixed. No testing to delineate type of neuropathy. Neuropathy: diabetic-128, other-144 patients No specified criteria for entry delineated. Balance impairment w Tinetti score \leq 23: 250 patients Pain \geq 4 on VAS: 256 patients	Monofilament (unspecified device used on 5 unspecified plantar sites) VAS (only in those w scores of \geq 4) Tinetti Tool (only in those w scores \leq 23 at t=0)	Diode (Anodyne) ??-??-890 nm AND Physical therapy
Yongzhan, Wenying, Wenming, Yanbing, Jianping, Yinxing, Zhihong	Paper	2005	No	China	Presumed peripheral diabetic neuropathy (type 1 or 2 diabetes) Excluded patients w edema or fracture	NCV (nerve conduction velocity-unspecified sensory nerves) Current perception threshold-unspecified frequency) Monofilament (unspecified device) Tuning fork (unspecified frequency) Patellar reflex	(Anodyne) ??-??-890 nm

						Pain scales-Unspecified x2	
Jie, Yangcheng, Jiazhong, Haohua, Shuxin, Xiaoqi	Paper	2005	No	China	Presumed peripheral diabetic neuropathy (type 1 or 2 diabetes)	Monofilament (for fine touch, not pressure) Temperature (not standardized) Michigan Neuropathy Screening Instrument (Unspecified segment)	Diode (Anodyne) ??-??-890 nm
DeLellis, Carnegie, Burke	Paper	2005	Yes	USA	Presumed diabetic neuropathy Excluded patients w ICD9 code 357	Monofilament (unspecified device used on 5 plantar sites)	Diode (Anodyne) ??-Pulsed-890 nm
Predergast, Mirada, Sanchez	Paper	2004	Yes	USA	Mixed neuropathy. No testing to delineate type of neuropathy Neuropathy: diabetic-21, other-6 patients No specified criteria for entry delineated.	Current perception threshold at 3 frequencies	Diode (Anodyne Model 480) ??-Pulsed-890 nm
Leonard, Farooqi	Paper	2004	Yes	USA	Presumed peripheral diabetic neuropathy (type 1 or 2 diabetes) Required lack of sensation to 5.07 monofilament on at least 2 of 5 plantar sites & 3 metatarsal sites.	Monofilament (unspecified device) VAS MNSI questions Altered MNSI physical exam	Diode (Anodyne Model 480) GaAlAs-Pulsed-890 nm
Zinman, Ngo, Ng, Nwe, Gogov, Brill	Paper	2004	Yes	Canada	Painful diabetic neuropathy (type 1 or 2 diabetes) Diagnosis based on Toronto Clinical Neuropathy Score Excluded patients w pain <4 on VAS-McGill Excluded patients w unstable medical conditions including thyroid disease & alcohol use	VAS-McGill QST (quantitative sensory testing-pressure, vibration, temperature) NCV (nerve conduction velocity of peroneal, sural., sympathetic skin response in legs) w temp control	Laser (Theralase TLC 5000) ??-??-905 nm
Kochman	Paper	2004	No	USA	Mixed peripheral neuropathy No testing to delineate type of neuropathy. Neuropathy: diabetic-27, alcohol-6, vascular disease-5 patients Required hx of falling & unspecified high Tinetti scores	Monofilament (unspecified device) Tinetti Tool	Diode (Anodyne) ??-??-890 nm AND Physical therapy
Kochman, Carnegie, Burke	Paper	2002	Yes	USA	Presumed diabetic neuropathy (type 1 or 2 diabetes) No testing to delineate type of neuropathy No specified criteria for entry delineated.	Monofilament (series of monofilaments) Temperature (unspecified tool)	Diode (Anodyne) GaAlAs-??-??

??=Parameter for light therapy not provided QST=Quantitative sensory testing NCV=Nerve Conduction Velocity MNSI=Michigan Neuropathy Scoring Instrument VAS=Visual analogue score pain score

Table 6
Peripheral Neuropathy

Panel B

Author	Study Type	Randomized	Control	Blind	IRB	Consent	Patient Number	Funding Source
Arnall, Nelson, Lopez, Sanz, Iversen, Sanz, Stambaugh, Arnall	<i>Prospective</i> No indication of number rejected in screening Unspecified enrollment period	Random leg assignment	Other foot	Unclear Monofilament examiner blinded	Yes	Yes	22 patients 44 feet 1 site	Equipment provided by RevitaMed (1 author from GE Analytical Instruments)
Pappas	<i>Case Series</i> Unspecified time period	No	Self	No	NI	NI	3 patients	NI
Harkless, Delellis, Carnegie, Burke	<i>Prospective in reality</i> Said record review, but clinic notes obtained by un-named DME supplier prior to & after providing device. Data collection 1/04-11/04	No	Self	No	NI	NI	2812 records met ICD9 data 2239 records met clinical test criteria Diabetic-1395, other-844	Author Burke is the Anodyne Director of Research & Clinical Affairs Unlisted author, A Spirides, who provided statistical analyses and figures is the Anodyne Director of International Marketing Unlisted authors include staff of device suppliers
Powell, Carnegie, Burke (2005-6)	<i>Cross-sectional survey & Retrospective record review</i> Insurance records from 2 unspecified DME suppliers reviewed for lists of patients treated 1/02-3/02 Patients called $\geq 3x$	No 369 contacted 252 responded	Self	No	NI	NI	369 considered eligible 252 responded post $\geq 3x$ phone calls 8 interviewers	MedAssist=Anodyne Author Burke is the Anodyne Director of Research & Clinical Affairs
Clifft, Kasser, Newton, Bush	<i>Prospective</i> No indication of number rejected in screening Unspecified enrollment period 4 drop-outs.	Yes	Placebo Sham device	Double-blind (sham device)	NI	Yes	77 lower extremities 43 patients	MedAssist=Anodyne provided device
Volker, Hassan, Hassan, Smock, Connor, McFee, Ferguson, Burke	<i>Quasi retrospective</i> Reports retrospective review of 272 consecutive patients with neuropathy, but no indication of number rejected in screening Unspecified time period	No	Self	No	NI	NI	272 patients Diabetic-128, other-144 patients Tinetti score ≤ 23 : 250 patients VAS pain score ≥ 4 : 256 patients 7 sites including outpatient, nursing home, hospital	Anodyne Unlisted author, A Spirides, who provided statistical analyses and figures is the Anodyne Director of International Marketing
Yongzhan, Wenying, Wenming, Yanbing, Jianping, Yinxing, Zhihong	<i>Prospective</i> No indication of number rejected in screening Unspecified enrollment period	No States is random enrollment, but all patients treated	Self	No	NI	NI	30 patients 1 site	Anodyne contact information provided in article
Jie, Yangcheng,	<i>Prospective</i>	No	Self	No	NI	NI	35 patients	Anodyne contact information

Jiazhong, Haohua, Shuxin, Xiaoqi	No indication of number rejected in screening. Unspecified enrollment period						1 site	provided in article
DeLellis, Carnegie, Burke	Prospective in reality Claim record review, but providers given bf & after forms to complete as well as info on monofilament use. Record source=unnamed DME supplier. Records pulled for device use 2/02-1/04	No	Self	No	NI	NI	1047 records reviewed Neuropathy:diabetic-790, other-257 ?? number of sites	Author Burke is the Anodyne Director of Research & Clinical Affairs Unlisted author, A Spirides, who provided statistical analyses and figures is the Anodyne Director of International Marketing Unlisted authors include staff of device suppliers & >300 medical personnel
Predergast, Mirada, Sanchez	Prospective No indication of number rejected in screening. Time period 3/02-9/02	No	Self Subgroup of 10 patients w prior CPT measurement	No	NI	NI	27 patients 1 site	MedAssist=Anodyne provided funding & statistical package
Leonard, Farooqi	Prospective-2 phase trial Used patients w 6.65 or 5.07 monofilament insensitivity Unspecified time period	Yes, 1 foot laser, other sham. Severity stratified	Other foot placebo Sham device	Double-blind. (Sham device) Only for 1 st 6 tx	Yes	NI	54 feet 27 patients Insensate to 5.07-18 patients Insensate to 6.65-9 patients 1 site, 1 examiner	Device provide by Anodyne Authors have received laboratory funds from MedAssist
Zinman, Ngo, Ng, Nwe, Gogov, Brill	Prospective-3 phase trial No indication of number rejected in screening Enrolled 10/200-2/2001	Yes	Placebo Sham device	Double-blind (Sham device) QST & NCV performed by independent tester	Yes	Yes	50 patients 1 site	NI
Kochman	Prospective in reality 38 consecutive patients attending a PT clinic. No indication of number rejected in screening Unspecified time period	No	Self (History of falls in 3 months prior to evaluation.)	No	Yes	NI, Possibly NA	38 patients 1 site	NI
Kochman, Carnegie, Burke	Prospective No indication of number rejected in screening Unspecified time period	No	Self	No	NI	NI	49 patients 1 site, 1 examiner	NI

IRB=Institutional Ethics Review Board NI=Not indicated QST=Quantitative sensory testing NCV=Nerve Conduction Velocity

Table 6
Peripheral Neuropathy

Panel C

Author	Exclusion of Other Rx/Tx	Washout	Trial Duration	Regimen: Tx Duration	Regimen: Tx Frequency and Dose	Post-Tx Withdrawal Period/Evaluation	Results
Arnall, Nelson, Lopez, Sanz, Iversen, Sanz, Stambaugh, Arnall	No change in rx during study	No	8 weeks	8 weeks	30 minutes/tx 3x/week	No	No reported changes in temperature or vibratory sense Sites not uniformly tested (3-5 tests/site). Imbalance at baseline for 1 site. Statistical analysis incorrect. Did not compare between group changes & did not compare for multiple measures.
Pappas	No	No	8 weeks	4 weeks	30 minutes/tx 3x/week Tx given to calves as well as to feet	Yes 4 weeks post discontinuation	Improvements were reported for monofilament sensation, VAS, diabetic neuropathy score, & walking distance. Effects were reportedly maintained after tx withdrawal. Tests of statistical significance were not performed. Paired T- tests performed on the available data indicate that sensation, pain, & neuropathy scores did not differ between groups before & after treatment. Walking distances did differ (p=0.04).
Harkless, Delellis, Carnegie, Burke	No Rx continued	No	Unspecified	Unspecified	Unspecified	No	VAS pain & monofilament sensation improved after tx. Response did not differ by neuropathic etiology.
Powell, Carnegie, Burke (2005-6)	No	No	Unspecified Questioned 1-15 months post neuropathy improvement	Unspecified	Unspecified	Could still be using device	Reported decreased fear of falling, fall number, & pain. Reported some increase in ADL performance. Survey complicated by selection bias of those determined to be eligible as well as only 68% response rate.
Clift, Kasser, Newton, Bush	No (Speculation that better skin care led to improvement.)	No	8 weeks	4 weeks	1.95J/cm ² for 30 minutes 3 days/week x4 weeks	Yes 4 weeks post discontinuation	Monofilament sensitivity improved after placebo & experimental tx by ~30%. There were no substantive gains or losses in sensitivity after withdrawal of actual or sham therapy for 4 weeks. 2 burns occurred.
Volker, Hassan, Hassan, Smock, Connor, McFee, Ferguson, Burke	No	No	≥6 tx	≥6 tx	30 -60 minutes 3x week	No	Reported improvement in all categories (sensation, pain, balance) whether neuropathy due to diabetes or not.
Yongzhan, Wenying, Wenming, Yanbing, Jianping, Yinxing, Zhihong	No	No	10 treatments	10 treatments	48 J/cm ² in 30 minute sessions	No	Reports improvement in all categories.
Jie, Yangcheng,	No change in	No	≥4 weeks	≥4 weeks	30 minutes	No	Reported improvement for monofilament & MNSI.

Jiazhong, Haohua, Shuxin, Xiaoqi	diabetic management during study		Data after 6 & 12 visits		1x/every other day		No statistical testing done on temperature sensation.
DeLellis, Carnegie, Burke	No	No	Unspecified	Unspecified	Unspecified	No	Reported decrease in number of pedal sites insensate to monofilament from 7.9 to 2.3; p<0001. Response per etiology not reported.
Predergast, Mirada, Sanchez	No change in rx during study	No	2 weeks	2 weeks	40 minutes/tx 10 treatments over 2 weeks (1 patient received 5)	No	CPT scores tended to increase over time w/o tx (p=0.16), but no correlation data were presented. CPT scores for the subgroup improved only for 2000 Hz (p=0.03). CPT scores for the entire group improved for 2000 & 250, but not 5 hz (p<0.001 & <0.02)
Leonard, Farooqi	No	No	4 weeks	2 wks controlled-> 2 wks both feet actively treated.	1.3J/cm ² 40 minutes/tx. 3x week	No	Reported improvement in the less severely affected group, but not the severely affected group even with additional therapy during the unblinded phase. Reported improvement in pain & the questionnaire. The modified MNSI exam did not differ by tx. The analyses are flawed because they compared only the parameters at baseline & 6 or 12 weeks. They did not directly compare the parameter deltas for the active and sham tx. The study did not identify the magnitude of sensory change that would be clinically significant. The longitudinal improvements for several parameters over time suggest a large placebo effect.
Zinman, Ngo, Ng, Nwe, Gogov, Bril	Could not change analgesic rx for at least 1 month prior to study entry & during study	No rx change allowed. Sham tx for 2 wks prior to randomization.	8 weeks	2 wks sham --> 4 wks tx --> 2 wks withdrawal	5 min/site 2x/ week	2 wk withdrawal- no blind	Change in pain did not reach statistical significance. Sham tx appears to initially decrease pain ~25%. Washout suggests that effects on pain might wane. The other test parameters did not change w tx.
Kochman	No	No	Variable	Variable Number tx based on severity of imbalance	30-40 min/daily 6-20 tx	3 month post treatment interview for falls	Monofilament sensitivity & Tinetti score improved (p <0.001) Reported decreased fall risk, but limited statistical data. No tx arms to assess impact of physical therapy.
Kochman, Carnegie, Burke	No change in circulation rx for 30 days prior to study entry. No change in glucose control tx.	No	30 days	30 days	2 of 4 diode arrays placed over pedal arteries 30 minutes/tx 12 treatments	No	Baseline monofilament insensitivity no different for type of diabetes. Response to tx no different by type of diabetes. Reported decrease in monofilament insensate areas. No statistical evaluation of temperature data.

Rx=Medications Tx=Treatment NI=Not indicated VAS=Visual analogue pain scale J=Joules

Table 7

Placebo-Controlled Studies of Infrared Monotherapy for Wound Healing

			Baseline			End Treatment				
			Active	Placebo	Between Groups	Active	Δ Delta	Placebo	Δ Delta	Between Groups
Venous	Franek*	Absolute Wound Area-cm ²	15.76	13.25	P=NS	11.51	4.25	8.04	5.21	P=NS
		Absolute Volume Size-cm ³	3.67	3.26	P=NS	2.05	1.62	1.65	1.61	P=NS
	Malm	Healed ulcers at 12 weeks	21	21		13 healed 4 withdrawals	4 not healed	11 healed 6 withdrawals	4 not healed	P=NS
Pressure	Lucas-2003	Absolute Wound Size-mm ²	246	338	P=NS	194	-48	200	-138	P=NS
		Relative Change Wound Size-%	NA	NA			-5		-34	P=NS
	Lucas-2000	Median Absolute Wound Size mm ²	94	82.5	P=NS	16	-78	4	-78.5	P=NS
Surgical	Lagan-2001	Relative Change Wound Size-% By photo or planimetry	100	100			-98-99		-100	P=NS
		Pain Score	100	100			- ~40		- ~45	P=NS
	Palmgren	Daily Healing rate-cm ²	NI	NI		2.45		1.65		NI
		T1/2 to healing-days	NI	NI		6.8		14.0		

NS=Not statistically significant NI=Not indicated

*The study had 2 control groups: 1 with sham treatments and 1 without. Only the data from the sham treatments were included for brevity

NI

Table 8

Placebo-Controlled Studies of Infrared Monotherapy for Peripheral Sensory Neuropathy

		Pre-Treatment Phase (t=0)			Baseline (t=1) (Absolute Value, [Delta Value])					Treatment End (t=2) (Absolute Value, [Delta Value])					Post Treatment Phase (t=3) (Absolute Value, [Delta Value])				
		Act	Plac	Btwn groups	Act	Δt1-t0	Plac	Δt1-t0	Btwn groups	Act	Δ t2-t1	Plac	Δ t2-t1	Btwn groups	Act	Δ t3-t2	Plac	Δ t3-t2	Btwn groups
Cliff	# Sensate Points of 4				0.57	NA	0.85	NA	P=NS	0.94 [0.47]	P <0.002	1.42 [0.57]	P <0.05*	P=NS	1.17 [0.17]	P=NS	1.54 [0.12]	P=NS	P=NS
Zinman	Pain Score	7.1	6.9	NS	5.8 [-2.4]	NI	5.4 [-1.5]	NI	NI	4.7 [-1.1]	NI	5.4 [0.0]	NI	P=NS	5.2 [0.5]	NI	5.6 [0.2]	NI	P=NS
	Toronto Test									NI		NI		P=NS					
	QST									NI		NI		P=NS					
	NCS									NI		NI		P=NS					
															Act	Δ t3-t1	Plac	Δ t3-t1	Btwn groups
Leonard <severe	# Insensate Points of 5				3.5	NA	3.6	NA	P=NS	2.4 [-1.1]	P<0.02	3.0 [-0.6]	P<0.09	NI	1.9 [-1.6]	P<0.001	2.3 [-1.3]	<0.002	NI
	MNSI-Q				4.7	NA	4.7	NA	NI	3.5 [-1.2]	P<0.0001	3.8 [-0.9]	P<0.01	NI	3.2 [-1.5]	P<0.0001	3.7 [-1.0]	P<0.05	NI
	MNSI-E				1.5	NA	1.6	NA	NI	1.4 [-0.1]	P=NS	1.3 [-0.3]	P=NS	NI	1.3 [-0.2]	P=NS	1.3 [-0.3]	P=NS	NI
Leonard >severe	# Sensate Points of 5				4.7	NA	4.4	NA	P=NS	4.0 [-0.7]	P=NS	4.0 [-0.4]	P=NS	NI	3.7 [-1.0]	P=NS	3.9 [-0.5]	P=NS	NI
	MNSI-Q				3.7	NA	3.6	NA	NI	3.0 [-0.7]	P=NS	3.3 [-0.3]	P=NS	NI	3.0 [-0.7]	P=NS	3.1 [-0.5]	P=NS	NI
	MNSI-E				2.1	NA	2.1	NA	NI	1.9 [-0.2]	P=NS	1.9 [-0.2]	P=NS	NI	1.8 [-0.3]	P=NS	1.8 [-0.3]	P=NS	NI

*but unspecified Act=Active treatment Plac=Placebo treatment Btwn=Between NS=Not statistically significant NI=Not indicated NCS=Nerve Conduction Studies QST=Quantitative Sensory testing Toronto Test=Toronto Clinical Neurology Score

Appendix D

Jeffrey Basford, M.D., Ph.D. Letter

Gayle Reiber, Ph.D. , M.P.H. Letter



May 19, 2006

Louis Jacques, M.D., Director
 Division of Items and Devices
 Coverage and Analysis Group
 Office of Clinical Standards and Quality
 Dept. of Health and Human Services
 Centers for Medicare and Medicaid Services
 7500 Security Blvd, Mailstop C 1-09-06
 Baltimore, MD 21244-1850

200 First Street SW
 Rochester, Minnesota 55905
 507-284-2511

Jeffrey R. Basford, M.D., Ph.D.
 Physical Medicine and Rehabilitation
 507-255-8972 Fax 507-255-7696

Dear Doctor Jacques:

I recently received your letter requesting my comments on the "role of infrared therapy and wound healing and neuropathy as well as on what conclusions, if any, are supported by the available data." This is an area of particular interest of mine, and I am happy to provide you with my thoughts.

It is important to know a person's background when you judge their comments. My initial training was in experimental physics, and I have been a board certified physician of Physical Medicine and Rehabilitation since the early 1980s. I am currently a Professor in the Mayo Clinic's Department of Physical Medicine & Rehabilitation, and the majority of my medical care and research has involved the influences of physical forces on the body. In particular, I have been involved in investigating the potential clinical benefits of light-based therapy (e.g., low energy laser, low intensity laser, infrared (IR)) for more than 20 years. I have performed multiple studies in this area and have published their findings in the peer-reviewed literature. (Please see my attached CV.)

As you know, mankind has been intrigued by light-based therapy for more than 2000 years. However, current interest in the non-thermal aspects of light, and specifically the IR and near-IR spectrum, began in the mid-1960s following reports by Endre Mester that Helium-Neon (HeNe) laser irradiation appeared to speed the healing of lower extremity ulcers. Doctor Mester's reports included large subject numbers but, unfortunately, little or no blinding or controlled evaluation. Interest was initially centered in Eastern Europe and the former USSR. However by the 1970s, investigations became frequent in Western Europe and subsequently Asia and the US. I would like to cite a definitive article or two to clarify the benefits of light and non-thermal IR therapy. Unfortunately, the literature is too diverse, limited, and underpowered to permit this. I can, however, summarize the situation and perhaps direct your attention to some pertinent literature.

I believe that most people accept that light produces effects at the level of cellular function that are dependent on wavelength and are not the result of heating. Unfortunately, translation of these results to animals and humans has been difficult with many experiments showing benefits and others showing little or no effect. Initial research typically involved low power HeNe lasers as noted above as well as other devices such as Argon and Krypton lasers. However, once superluminous and laser diodes became available, efforts focused on red and IR radiation due to cost, ease of use, improved tissue penetration and reports of benefits. Soft tissue injuries, wounds, and pain have consistently been the center of experimental and research interest.

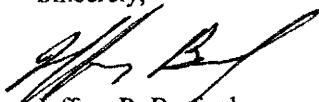
Research in the US began in the late 1970s, and in 1985, an FDA Pre-Market Approval (PMA) Review Panel reviewed the effects of HeNe laser irradiation on rheumatoid arthritis. The panel concluded that evidence of efficacy was too limited to permit a recommendation of acceptance. I performed my last published review in 1995 (see CV) and concluded the field had exciting possibilities but that clinical benefits had yet to be established. Research has improved continued subsequently with numerous investigators finding benefits: again with the most marked finding at the basic science level and with difficulty obtaining overwhelming evidence of clinical benefits.

Many in the field may consider me conservative in this assessment. However, I reviewed the Cochrane Database for this topic while writing this letter and confirmed that members of this collaboration find little or no support for the use of light therapy for osteoarthritis, lower extremity venous stasis ulcers or tuberculosis and only weak support for the treatment of rheumatoid arthritis. The overall assessment is that better designed, controlled, and powered studies are needed.

Currently about 22 devices have FDA approval. On first look, this seems to be impressive; but unfortunately, this acceptance has not been on the basis of a PMA assessment but due to the 2002 relaxation of the requirements to that of a 510K process on the basis of use as an adjunct in the treatment of pain their being "substantially equivalent" to "pre-Amendment" IR treatments.

I wish I could be more optimistic about the certainty of clinical benefits at this time. I am convinced that the numerous reports of established investigators at the cellular (e.g., T. I. Kuru), animal (J. Anders among others), and even human spinal cord (S. Rochkind et. al.) describe real findings. However, I believe that the extension of these findings to the demonstration of significant and strongly supported clinical benefit has not yet occurred. This difficulty is not unique to light and nonthermal IR therapy-it is shared by many physical treatments and includes issues such as the semi-quantitative nature of pain, choice of appropriate outcome variables, and the natural fluctuations of pain in many of the conditions studied. In addition, dosage is important as light is attenuated as it passes through tissue. In particular: what dose is too low and is a dose $> 1-4 \text{ J/cm}^2$ often recommended detrimental? (The World Association of Laser Therapy Website (<http://www.walt.nu>) presents a systematic review and recommendations for this issue.)

Sincerely,



Jeffrey R. Basford

JRB:cab



University of Washington
Seattle, Washington 98195-7660

School of Public Health and Community Medicine

Department of Health Services
Box 357660
FAX: 206-543-3964

July 24, 2006

Louis Jacques, MD
Director
Division of Items and Devices
Coverage and Analysis Group
Centers for Medicare & Medicaid Services
7500 Security Boulevard, MS C1-09-06
Baltimore, MD 21244-1850

Dear Dr. Jacques:

Thank you for your request for an expert opinion from our clinical research group on the role of infrared therapy for individuals with diabetic peripheral neuropathy and diabetic ulceration. My research group includes vascular and orthopaedic surgeons, internal medicine physicians, podiatrists, dermatologists, epidemiologists and biostatisticians.

We reviewed the published evidence on infrared therapy and diabetic peripheral neuropathy. Uncontrolled studies show a beneficial effect from monochromatic infrared energy on peripheral sensation.¹⁻³ However, without a suitable placebo control group, inferences cannot be made on the device efficacy. Two randomized, double-blind, placebo-controlled trials came to differing conclusions. The first by Leonard, et al.⁴ was designed with the primary outcome being change in sensitivity to the 5.07 monofilament. There was no a priori hypothesis regarding differences between 5.07 and 6.65 monofilaments. Nor was there a priori specification of subject stratification based on initial monofilament response. The randomized treatment protocol delivered ATS Model 480, Anodyne Therapy System (ATS) three times per week for 40 minutes for two weeks. Then unfortunately the randomized design collapsed and all subjects received ATS treatment for an additional two weeks. The controlled data for the first two weeks is presented in two strata, and the intent-to-treat analysis is not clearly presented. Leonard and colleagues report important findings in the paper for the two-week treatment, including decreased pain, and improved balance. Nothing can be stated for the interval for which there are no control data. Thus we can say little about efficacy.

The Clifft study⁵ randomized 39 subjects with diabetic peripheral neuropathy of varying severity to an eight-week of study of monochromatic infrared energy (MIRE) three times per week for eight weeks

with monofilament measures at baseline, 4 and 8 weeks. This well-designed study found no difference between intervention and control subjects in sensitivity to the 5.05 monofilament at the trial conclusion.

Diabetic peripheral neuropathy represents neuronal death. Nerve regeneration down the axonal tube is possible, but this reinnervation takes from months to years. Two to eight weeks is not sufficient for this process to occur. Thus additional studies on this potential therapy are needed that are more specific in terms of therapeutic interval, dose, placement of therapy pads, and threshold levels. Subjects should be more homogenous in terms of type of diabetes and severity of neuropathy.

If I can provide additional information, please let me know. Our team is looking forward to future research in this area.

Sincerely,



Gayle E. Reiber, MPH, PhD

VA Career Scientist

Professor, Departments of Health Services and Epidemiology

University of Washington

1. Horwitz LR, Burke TJ, Carnegie D. Augmentation of wound healing using monochromatic infrared energy. Exploration of a new technology for wound management. *Adv Wound Care*. Jan-Feb 1999;12(1):35-40.
2. Kochman AB, Carnegie DH, Burke TJ. Symptomatic reversal of peripheral neuropathy in patients with diabetes. *J Am Podiatr Med Assoc*. Mar 2002;92(3):125-130.
3. Kochman AB. Monochromatic infrared photo energy and physical therapy for peripheral neuropathy: influence on sensation, balance, and falls. *J Geriatr Phys Ther*. 2004;27:16-19.
4. Leonard DR, Farooqi MH, Myers S. Restoration of sensation, reduced pain, and improved balance in subjects with diabetic peripheral neuropathy: a double-blind, randomized, placebo-controlled study with monochromatic near-infrared treatment. *Diabetes Care*. Jan 2004;27(1):168-172.
5. Clift JK, Kasser RJ, Newton TS, Bush AJ. The effect of monochromatic infrared energy on sensation in patients with diabetic peripheral neuropathy: a double-blind, placebo-controlled study. *Diabetes Care*. Dec 2005;28(12):2896-2900.

Appendix E

Mechanistic Studies for Infrared Technology

The mechanisms by which healing or pain relief might occur are still unknown. The existing information, on its face, is contradictory. For this reason, it has not been possible to identify the specific features of irradiation devices and treatment regimens that are critical to efficacy.

Changes in tissue temperature are not thought to be contributory by most investigators (Maegawa, Ohshiro), but the data are conflicting. Indeed some investigators have found tissue cooling whereas others have found tissue heating (Lowe 1994, Schindl 1998, 2002). Unfortunately such thermal changes have not been rigorously studied or excluded in most studies so it is not possible to reconcile the divergent results.

It frequently claimed that wavelengths in the red and near-infrared range improve circulation because increases in local blood flow have been documented by thermography and dynamic contrast-enhanced magnetic resonance imaging (Benedicenti, Schaffer, Schindl 1998, 2002). The underlying mechanism mediating blood flow remains unknown. A role for nitric oxide is frequently touted because it relaxes vascular smooth muscle and inhibits platelet cell function (Chen) and because constitutive (basal) nitric oxide synthase activity is impaired in diabetic patients (Martina). Meticulous work suggests that nitric oxide plays a relatively small role in vasodilation after irradiation (Maegawa). Although vasodilation was observed in exteriorized mesenteric arterioles of living rats, the addition of a nitric oxide synthase inhibitor did not alter peak blood flow or effect duration after irradiation. Power dependent calcium ion influx and calcium ion dependent ATPase in arterial endothelium and smooth muscle is a putative vasodilatory pathway (Nasu). Irradiation-induced hyperpolarization of superior ganglion cells, if present in vascular smooth muscle cells, would be an alternative vasodilatory mechanism (Maegawa, Shimoyama).

Others have attributed healing to effects on the immune system. In septic rats exposed to argon dye laser light (630 nm), there was improved survival, lymphocyte proliferation, and enhanced ATP synthesis by lymphocytes (Yu). These effects, however, cannot be easily extrapolated. *In vitro* lymphocytes exposed to the mitogen, phytohemagglutinin, proliferated after high energy density, but not after low energy density irradiation by an gallium aluminum arsenide (GaAlAs) laser (Inoue). Similarly, *in vitro* macrophages exposed to non-coherent light (660, 870, and 880 nm) released proliferative growth factors, but not when exposed to coherent and polarized light (880 nm) (Young).

Other investigators have postulated that healing is mediated by fibroblast proliferation and increased collagen production by fibroblasts. Exposure of monolayer cultured fibroblasts to LED (905 nm) or GaAlAs laser (830 nm) irradiation increased cell number within 24 hours (Vinck). Treatment of full thickness experimental bovine teat wounds with helium-neon (HeNe) laser (632.8 nm, continuous wave) resulted in collagen that was thicker, denser, and more contiguous with pre-existing collagen fibers (Ghamsari).

Treatment of surgically induced wounds in pigs and hairless mice with HeNe laser increased types I and II pro-collagen mRNA (porcine), collagen (murine), and tensile strength (murine) (Lyons, Saperia). These effects, however, cannot be easily extrapolated. Initial increases in fibroblast number were eliminated by prolonged cell incubation (Vinck). Similarly, fetal mouse limbs irradiated by GaAs laser (904 nm) exhibited attenuated growth despite increased cell number and collagen fiber thickness (Thawer 1999).

Still others have hypothesized that selective spectral absorption by intracellular proteins impacts cell function and energy metabolism (Cooper, Karu 1989, 2005). Cytochrome c oxidase, a terminal enzyme in the electron transfer chain is one such protein. Irradiation of cultured neurons blunted the toxic effects of potassium cyanide on cytochrome c oxidase activity, cellular ATP content, and cell viability (Wong-Riley). These protective effects cannot easily be extrapolated. Responses appear to depend on the cyanide dose, metabolic class of neurons, and light wavelength (Wong-Riley). In addition, other toxins such as sodium azide appear to be activated by irradiation (Karu 2004). Consideration of other photoacceptor molecules complicates the picture. If irradiation increases or translocates nitric oxide, which is an inhibitor of cytochrome c oxidase, the net result on tissue metabolism and the whole organism cannot easily be predicted (Cooper, Jia, Kosako, Lancaster, Padron, Sharp, Stamler). Interactions with other photoacceptor molecules, such as hemoglobin and myoglobin, compound the problem further.

Because this putative therapeutic modality encompasses a diverse field of devices, any therapeutic efficacy may depend on a variety of factors including the light source, spectral range, power level, power density, degree of light coherence, constancy or pulsatility of the light beam, pulse repetition frequency, pulse duration (duty cycle), frequency of treatment, duration of each treatment, dose, duration of therapeutic regimen, disease entity (type of wound or nerve damage), and target tissue. For example, changes in median nerve conduction observed after irradiation with GaAlAs 830 nm continuous light were ablated when the light was pulsed and the wavelength changed to 820 nm (Lowe 1994, 1995). Similarly, changes in nerve conduction observed after 1.5J/cm² of radiant exposure to GaAlAs 830 nm light were not seen with higher radiant exposures (3-12J/cm² (Lowe 1994). Indeed these higher doses trended towards opposite effects on conduction latency. Furthermore, more distal irradiation of the median did not have the same effect as more proximal or local irradiation on conduction (Baxter 1994). In the same way, transient increases in blood flow were observed after indium gallium arsenide (InGaAs) (670 nm; 0.12-0.36 J/cm²) radiant exposure, but not after other light irradiation (HeNe laser exposure; 632.8 nm; 0.01 J/cm² or monochromatic light; 635 nm; 0.68-0.136 J/cm²). Such divergent results suggest that therapeutic efficacy, if any, is dependent on a multitude of variables and cannot be extrapolated easily to other devices and diseases (Basford, Baxter 1991, 1994, Greathouse, Lowe 1994, 1995, Snyder-Mackler, Walsh).

Appendix F

FDA Warning Letters