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A Randomized Controlled Trial of Skin Care Protocols for Facial Resurfacing: Lessons Learned from the Plastic Surgery Educational Foundation's Skin Products Assessment Research Study

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Abstract

Background—The Skin Products Assessment Research (SPAR) Committee was created by the Plastic Surgery Educational Foundation (PSEF) in 2006. SPAR study aims were to (1) develop an infrastructure for PSEF-conducted, industry sponsored research in facial aesthetic surgery and (2) test the research process by comparing outcomes of the Obagi Nu-Derm System (ONDS) versus conventional therapy as treatment adjuncts for facial resurfacing procedures.

Methods—The SPAR study was designed as a multi-center, double-blind, randomized controlled trial (RCT). The study was conducted in women with Fitzpatrick type I-IV skin, moderate to severe facial photo damage, and peri-ocular and/or peri-oral fine wrinkles. Patients underwent chemical peel or laser facial resurfacing and were randomized to ONDS or a standard care regimen. The study endpoints were time to re-epithelization, erythema, and pigmentation changes.

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FINANCIAL DISCLOSURE AND PRODUCTS PAGE None of the authors has a financial interest in any of the products, devices, or drugs mentioned in this manuscript.

Results—Fifty-six women were enrolled and 82% were followed beyond re-epithelization. There were no significant differences in mean time to re-epithelialization between ONDS and control groups. The ONDS group had a significantly higher median erythema score on day of surgery (after 4 weeks of product use) which did not persist after surgery. Test-retest photo evaluations demonstrated that both inter- and intra-rater reliability were adequate for primary study outcomes.

Conclusions—In a clinical RCT, we demonstrated no significant difference in time to re-epithelization between patients who used the ONDS or a standard care regimen as an adjunct to facial resurfacing procedures. The SPAR research team has also provided a discussion of future challenges for PSEF sponsored clinical research for readers of this article.

BACKGROUND

As the “Baby Boomers” age, plastic surgeons have seen dramatic growth in demand for cosmetic surgery and skin care services. The American Society of Plastic Surgeons (ASPS) estimates that its members performed over 10.4 million minimally invasive cosmetic procedures in 2008, nearly double the number performed only eight years earlier 1.

Many facial aesthetics procedures are based on scientific evidence which is fundamentally flawed. A recent 10 year review of major plastic surgery journals, including *Plastic and Reconstructive Surgery*, *Annals of Plastic Surgery*, and *The Aesthetic Surgery Journal*, identified a total of 1419 published clinical studies in aesthetic surgery. Of these, 86% were uncontrolled, consisting of case reports, case series or expert opinions. Only 3% of the studies used randomized controlled trial (RCT) designs 2.

Patient satisfaction, body image, and quality of life are major determinants of patient success. Despite this fact, a recent review of the aesthetic surgery peer-reviewed literature 3 noted that survey assessments of these outcomes had not achieved widespread use. More recently, Kosowski and colleagues conducted a systematic review of published patient reported outcomes measures (PROMs) for facial cosmetic surgery. All measures identified were limited by their development, validation or content. None of the instruments satisfied all guidelines outlined by the U.S. Food and Drug Administration 4 and the Scientific Advisory Committee of the Medical Outcomes Trust 5 for the development and validation of health outcomes questionnaires 6.

To promote a more evidence-based approach in aesthetic surgery, the Plastic Surgery Educational Foundation (PSEF) created a multi-center clinical trials network in 2006. Obagi Medical Products (Long Beach, California) made an unrestricted $100,000 grant to the PSEF to build the clinical trials network and to fund a pilot project for facial aesthetic surgery outcomes research. The agreement stipulated that the research would be conducted and controlled by the PSEF. Obagi Medical Products would have no influence on study design or publication of the data 7.

The Obagi Nu-Derm System (ONDS) is a tretinoin and hydroquinone-based skin health system produced by Obagi Medical Products. In a 24 week randomized control study, the ONDS was compared to three prescription and over-the-counter skin care regimens. The study included 387 middle-aged women with Fitzpatrick type I to type IV skin. Outcomes of interest included fine wrinkles in the periorbital and periocular region, skin clarity, and degree of mottled hyperpigmentation. Skin sallowness, laxity, and roughness were also included among study outcomes. At 24 weeks, the ONDS-treated patients had increased epidermal thickness and decreased hyperpigmentation. Additionally, statistically significant improvements in perioral fine wrinkles, skin laxity, mottled hyperpigmentation, and dermal thickness were seen when compared to other skin care regimens 8.

The proprietary ONDS *Cleanser*, *Toner*, and *Exfoderm Forte* components are hypothesized to improve epidermal permeability and improve delivery of both tretinoin and hydroquinone. Additionally, the ONDS has been shown to significantly increase dermal density when compared to other skin care regimens 8. These factors may reduce post-inflammatory hyperpigmentation and improve healing after chemical peel and/or laser facial resurfacing. Although the efficacy of the ONDS has been demonstrated for facial photo damage, the system could theoretically improve outcomes after resurfacing procedures.

The PSEF Skin Products Assessment Research (SPAR) Committee, under the leadership of Susan Kaweski MD, was charged to select a study team, formulate specific aims and methodology, recruit study centers and implement the study protocol. Dr. Ed Wilkins and Dr. Andrea Pusic were designated as the study's co-principal investigators. By mid-2006, the project protocol was complete and institutional review board approval had been received. The aims of the SPAR study were to (1) develop an infrastructure and process for PSEF-conducted, industry sponsored research in facial aesthetic surgery and (2) test the research process by comparing outcomes of the Obagi Nu-Derm System versus conventional therapy as treatment adjuncts for chemical peel or laser facial resurfacing.

METHODS

This study has been uploaded to www.clinicaltrials.gov (identifier NCT01113606). The SPAR Study was designed as a multi-center, double-blinded, randomized controlled trial. The primary study goal was to compare time to reepithelization, erythema, and pigmentation changes between patients using the ONDS versus a standard care regimen both before and after a facial resurfacing procedure. Eligible patients were in good overall health with Fitzpatrick I, II, III, or IV skin types. Patients were willing to avoid direct sunlight, including tanning beds, for the study duration. All had moderate to severe facial photo damage and peri-ocular and/or peri-oral fine wrinkles, as determined by a clinical grader.

Eligible patients were scheduled for either full or partial face resurfacing with chemical peel or ablative laser as a single operative procedure or as an adjunct treatment during other surgical procedures. The resurfacing procedure was chosen by the surgeon and was not randomized as part of the study protocol. Patients who had used topical prescription steroids, retinoids, depigmentation products or other products containing hydroquinone or poly-hydroxy acids within eight weeks of enrollment were excluded. Patients with severe acne, eczema, rosacea, or psoriasis were excluded. Additionally, any patient with known allergy to any topical skin care product, who had used isotretinoin within 12 months, or who was currently using photosensitizing drugs (thiazides, tetracyclines, fluoroquinolones, phenothiazines, or sulfonamides) was excluded.

Fitzpatrick skin type (I-IV) was determined at the initial patient visit, along with demographics such as age, smoking history, marital status, education and ethnicity. Additional independent variables including study site and procedure type were collected. After providing informed consent, patients were randomized to either the ONDS or standard care regimen (control) group. Block randomization was performed in groups of four using a random number generator. The ONDS or control products were provided to patients in de-identified, opaque plastic bottles. Instructions for product use referenced "bottle A" or "bottle B" as opposed to product name. Both patients and physicians were blinded to group for the duration of the study.

The standard care regimen for this study consisted of Cetaphil (Galderma Laboratories, Fort Worth, Texas) wash, Neutrogena Sunscreen Protection SPF30 (Neutrogena Corporation, Los Angeles, California), tretinoin, and hydroquinone. The pre-procedure standard care

regimen consisted of Cetaphil wash, 4% hydroquinone, and Neutrogena Sunscreen Protection SPF30 every morning and Cetaphil wash and 0.05% tretinoin application each evening. The regimen was applied to the whole face and was performed for 4 weeks prior to procedure. After re-epithelization had occurred, the same morning and evening regimen was continued until ten weeks after the procedure.

The ONDS regimen consisted of morning and evening use of the ONDS and was augmented by morning application of SPF 35 sunblock and evening application of 0.05% tretinoin. This regimen was initiated four weeks prior to the planned procedure. The same regimen was continued after re-epithelization had occurred until ten weeks after the procedure. As with the standard care regimen, the ONDS was applied to the whole face. Treatment regimens are summarized in Tables 2 and 3.

The treatment regimen between day of surgery and re-epithelization was not standardized as part of the SPAR study. Surgeon preference dictated treatment regimen during this time period.

The study was conducted between January 2007 and January 2008. Multiple centers were recruited to ensure adequate patient enrollment. Seven private practice plastic surgeons from a geographically diverse area contributed patients to the study. At each location, participating surgeons and their staff received training on study protocols and data management. To facilitate data collection, a password-secured SPAR website was developed and maintained by Data Harbor Solutions (Hinsdale, Illinois). Study investigators and participating centers accessed the site to upload patient data, including photographs. Patient surveys were completed by the study subjects via a separate password-secure portal on the website.

Patients were followed for a total of 14 weeks, including four weeks prior to and ten weeks after surgery.

Outcome Assessment

Clinical Photographic Assessment—The study's primary dependent variable of interest, time to re-epithelialization, was assessed using digital images of the affected facial areas. Images were collected at eight scheduled visits, ranging from four weeks pre-procedure to 10 weeks post procedure (see Table 4 for data collection schedule). Photos were also used to evaluate other outcome variables, including erythema, hyper-pigmentation, and hypo-pigmentation at all visits. Three board-certified plastic surgeons individually evaluated patient photos. Surgeons who reviewed photos did not contribute patients to the study and were blinded to subject's group assignment. Inter-rater reliability of the tele-evaluators was established with test-retest analysis performed in conjunction with the larger study. Time to re-epithelization was graded in days. Erythema, hyper-pigmentation, and hypopigmentation were graded using a none/mild/moderate/severe scale.

Patient Reported Outcomes—Previously validated questionnaires were used to measure patient-reported outcomes including symptoms, pain, aesthetic satisfaction, and quality of life both before and after procedures. Additional questions were developed to address patient demographics, product satisfaction and product usability. The following self-report questionnaires were employed: the Dermatology Life Quality Index (DLQI), Skindex-29, and the Brief Pain Inventory—Short Form (BPI-SF). In addition, the Medical Outcomes Study Short Form 12, version 2 (MOS SF-12 v2) was administered at the first and last visits to evaluate baseline and final physical and mental health summary scores. Patient satisfaction with the ONDS or standard care regimen was graded using a five point Likert scale.

Survey instruments were combined by visit according to protocol and collected from patients electronically via the study's website. Participating clinics provided subjects with a computer and a private space in which to complete their online questionnaires. Patients were also offered paper versions of the questionnaires when necessary; these were then entered into the study's database by SPAR staff. Data were stored remotely on a secure server during the enrollment and analysis period.

Statistical Analysis—Data analysis was performed using the Stata 11 statistical package (StataCorp LP, College Station, Texas). Time to re-epithelization between groups was examined using Student's t-test. Ordinal outcome variables, including erythema score, degree of hypo or hyper-pigmentation, and Likert scale ease-of-use results were analyzed using non-parametric statistics, specifically the Wilcoxon Rank Sum test. Significance level was set prior to the study as $p<0.05$. Test-retest analysis was performed to generate a measure of intra and inter-rater reliability. Kappa statistics were generated.

Prior to undertaking this project, study methodology was approved by Western Institutional Review Board (Olympia, Washington).

RESULTS

Fifty-six patients were enrolled from seven participating plastic surgery clinics. Ten patients (five from each group) were withdrawn because they were not followed until at least re-epithelialization. Reasons given for study withdrawal included unwillingness to wait four weeks before undergoing the resurfacing procedure, cancelled procedures, loss to follow-up and inability to follow the protocol, with no differences noted between groups. Overall, 82% of enrolled patients were followed beyond re-epithelialization.

Data on ethnicity, marital status, education level and Fitzpatrick skin type were collected as categorical variables. Analysis of these demographics indicated that the majority of subjects described themselves as "White, Non-Hispanic" women, married, and college graduates. The average reported Fitzpatrick Skin Type was "3" or "burn moderately, tan gradually". A non-statistically significant difference in age ($p=0.07$) was detected between groups (Table 1). No other demographic differences were noted.

Of the 46 patients who followed the study protocol, 22 were in the control group and 24 were in the ONDS group. Seventy four percent of all patients underwent laser resurfacing procedures, while the remaining 26% received chemical peels. Procedure types by treatment group are listed in Table 1.

Patients completed questionnaires regarding ease of product use and self-reported compliance on the day of procedure (after 4 weeks of product usage) and at two, six, and ten weeks after the procedure. Participants in both cohorts reported that the skin products were easy to use and not overly time consuming. The majority of patients in each group noted no discomfort from the products. No significant differences were detected between groups. Patient opinions about the regimen and associated discomfort were generally positive for both the ONDS and the control groups. No statistically significant group differences were noted for any of the responses at any of the time periods. As an illustration of the survey findings, group medians for the questionnaire items at Visit 8 (ten weeks post-procedure) are provided in Table 5.

Three independent board-certified plastic surgeons evaluated patient photos by answering four questions concerning the timing of re-epithelialization, the presence of erythema, and hyper- and hypo-pigmentation. A test-retest study of inter- and intra-rater reliability was

conducted to detect any differences between photo evaluators as well as differences over time. Kappa analysis performed on the test-retest photo evaluations indicated that both inter- and intra-rater reliability were adequate for evaluating re-epithelialization and erythema (kappa scores > 0.60). Reliability was lower when evaluating pigmentation before and after the procedures.

There were no significant differences in mean time to re-epithelialization between the ONDS and control groups (6.6 days vs. 7.3 days, p=0.63). Median erythema score was significantly higher on day of surgery (after 4 weeks of product use) in the ONDS group when compared to controls (mild erythema in the ONDS group and no erythema in the control group, p=.009). However, no significant differences in post-procedure erythema score were noted at any time point (Table 6). There were no significant differences between groups in levels of hyper or hypo-pigmentation.

DISCUSSION

The Role of Evidence-Based Medicine in Plastic Surgery

Randomized control trials represent the highest level of evidence and are considered the "gold standard" study design 9. However, current surgical practice is not necessarily based on high level evidence. A recent study showed that only 24% of surgical interventions are supported by RCT-derived data 10. Randomized control trials comprise between 0.3 and 3.7% of publications in other surgical subspecialties 11¯14. In 2003, a review of all articles in *Plastic and Reconstructive Surgery* demonstrated that 87% represented Levels 4 or 5 evidence; less than 6% provided Level 1 or 2 evidence 15.

Multiple authors advocate for improved study quality in the plastic surgery literature 2, 16. A trend towards higher level study designs has been noted over time 2, 15. However, simply relying on randomized, controlled trials does not guarantee high quality research. A recent review of RCT's published in major plastic surgery journals showed that studies had an average Jadad score (a systematic means of assessing RCT quality) of 2.3 out of 5, indicating low methodologic quality 17, 18.

Prior examinations of the aesthetic surgery literature have demonstrated that existing PROMs are under-utilized and poorly validated 3, 6. The BREAST-Q is a validated questionnaire to examine quality of life and outcomes after breast augmentation, reduction, and reconstructive procedures which has recently been developed 19, 20. Using a similar conceptual framework, both the FACE-Q and BODY-Q are now being developed and pilot-tested 21. These PROMs, when completed, will allow a more insightful view into patient satisfaction and quality of life after aesthetic and reconstructive procedures.

SPAR Study Findings

The skin care regimen to which patients were randomized had no significant effects on the outcomes of interest, with the exception of pre-procedure erythema. Furthermore, the difference observed in erythema, while statistically significant, may not be clinically relevant for most patients or providers. While our analysis did not detect significant differences in the treatments, it is possible that this finding is attributable to Type II error.

A properly conducted RCT randomizes a single variable. In our study, that variable was skin treatment protocol (control vs. ONDS). Randomization of a large population, when performed in a double-blind fashion, will create two groups of patients which are similar among identified and non-identified confounding variables. Review of procedural data (Table 1) demonstrates almost no differences in procedure types performed when stratified by group. The study was double-blinded and, as a result, surgeons performing the procedure

were unaware to which arm the patient had been randomized. We did not randomize procedure type as a component of this study, nor did we attempt to standardize the depth of wounding within procedures. Factors such as strength and duration of TCA peel application and number of passes with the laser could alter both time to reepithelization and erythema. However, we have no reason to believe that these factors would be different between groups, especially because the study was performed in a randomized, double-blinded fashion.

As a test vehicle for multi-center clinical trials in aesthetic surgery, the SPAR project was far more successful than its modest statistical analyses would indicate. The SPAR team built and feasibility-tested a network of centers and a centralized web-based data collection system. This infrastructure has served as a template for subsequent PSEF-sponsored clinical trials, including the current Venous Thromboembolism Prevention Study.

SPAR's most valuable product may actually be the knowledge gained by project investigators and PSEF leadership for the conduct of future multi-center clinical trials. During the SPAR study, the research team identified many challenges with implications for future research which are discussed below.

Future Challenges for PSEF-Sponsored Clinical Trials

Defining Roles and Responsibilities in Corporate-Sponsored Research—In the planning stages of SPAR, the PSEF and Obagi representatives struggled with issues surrounding control and study oversight. Issues of control over study design, protocols and results pose potential challenges for future research.

The SPAR project team believes that questions of study "ownership" should be carefully and explicitly negotiated prior to initiating any research conducted with the support of corporate donors. In instances of Foundation-initiated, corporate-sponsored studies, the research team and its study processes should be completely independent. For Foundation-initiated research, sponsors should be periodically updated on study progress but should not have decision-making roles in the project.

In the future, the PSEF may have opportunities to contract with biotechnology, pharmaceutical, or medical device manufacturers to conduct research trials on the company's behalf. Contract research endeavors will clearly be governed by different ground rules than Foundation-initiated research, as sponsors will likely formulate the hypotheses, aims, methods, and analytic design. In these instances, the sponsor will also control the study results. In this scenario, scientific priorities may conflict with the interests of the sponsor. As a result, these corporate relationships should be approached with extreme caution.

Promoting PSEF Membership Involvement in Clinical Trials—The success of PSEF-initiated research is dependent on surgeon's active participation in multi-center clinical studies. However, surgeon recruitment proved difficult due to the required time commitments. As investigators, we have endeavored to streamline study processes. The on-line data collection methodologies pioneered by SPAR and TOPS are initial steps towards this goal.

Recruiting sites for the project proved difficult, in part because the study did not address any major issues in clinical practice. Admittedly, the SPAR study was never designed to answer a critical issue in plastic surgery. Rather, the project was intended as a prototype study to develop and test methodologies for future multi-center clinical trials in aesthetic surgery. As

such, SPAR has been a success. Choosing research questions that surgeons really care about will be essential to building networks of practitioners for future studies.

Increasing Patient Recruitment for Clinical Trials—In virtually all clinical trials, patient recruitment lags behind expectations. However, without sufficient enrollment, cohort studies are under-powered to detect group differences and fail to adequately test the study hypotheses. Under-recruitment proved to be a significant issue for the SPAR Project. In designing the study, power calculations indicated that we needed a total enrollment of 80 patients (40 in each cohort) to detect group differences. At the conclusion of the project, we had obtained pre- and post-procedure data on little more than half that number.

To gain insights into this and other project issues, the study coordinator debriefed site principal investigators at the conclusion of the study. As one surgeon pointed out, recruiting aesthetic surgery patients for research is different than recruiting subjects for reconstructive studies. Aesthetics patients are likely less altruistic than other types of patients. Also, cosmetic patients are fairly affluent. It was the surgeons' impression that monetary compensation and product "giveaways" at the levels provided for SPAR proved ineffective in recruiting most subjects. In at least one of our centers, recruitment was hampered by a competing study in which the corporate sponsor offered far greater financial compensation for participating patients. Finally, we must understand that when patients seek out aesthetic surgery, they are motivated by a desire to improve their appearances, not by a need to help others.

Funding Research at Appropriate Levels—To succeed, multi-center clinical studies require significant financial and time resources. Despite simple methodology and having a realistic budget, SPAR was probably under-funded and study centers were insufficiently compensated. For future clinical trials, we recommend initial funding to cover the real costs to the sites of personnel and equipment. Salary support should be provided to fund a research assistant, responsible for patient recruitment and data collection, at each of the participating sites. In exchange for these resources, there should be clear (and written) agreement between the study investigators and the participating centers as to the site's responsibilities in the project. Finally, salary support for other key members of the project team (the PI, biostatistician, etc.) should be considered, given the considerable time demands of conducting multi-center trials.

CONCLUSION

For the most part, the plastic surgery literature consists of low-level evidence. With its ongoing research efforts, the Plastic Surgery Educational Foundation promotes high-quality, multi-center clinical trials. The SPAR study demonstrated few significant differences between skin care regimens used in conjunction with facial resurfacing. However, SPAR data demonstrated that research collaborations between the PSEF and corporate sponsors are possible and that multi-center research in plastic surgery is feasible. The knowledge and infrastructure from the SPAR study will benefit current and future multi-center trials sponsored by the PSEF.

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TABLE 1

Demographics and procedure type by group

	Control Group 22 patients	ONDS Group 24 patients
Mean age, years	55	49
Ethnicity, % of group		
White, non-Hispanic	88%	84%
Hispanic	8%	4%
Native American	0%%	12%
Asian	4	0%
Fitzpatrick Score, median	3	3
Smoking history		
Current	0%	4.2%
Previous	4.5%	4.2%
Procedure Type		
1% croton oil/phenol	5%	4%
TCA peel (20-25%)	9%	8%
TCA peel (30-35%)	13%	13%
Erbium laser	73%	75%

TABLE 2

Obagi Nu Derm System regimen

	Weeks 1 to 4		Procedure (Week 4)	Re-epithelialization to Week 8		Weeks 8 to 14	
	AM	**PM**		**AM**	**PM**	**AM**	**PM**
Foaming Gel Cleanser	X	X		X	X	X	X
Toner (adjusts skin pH)	X	X				X	X
Clear (4% hydroquinone)	X	X				X	X
Exfoderm Forte (alpha-hydroxy acids)	X						
Healthy Skin Protection (SPF-35)	X			X	X		
Blender		X					X
0.05% tretinoin		X					X
Sun Fader (SPF-15)						X	

* Italicized name indicates a trademarked component of the ONDS

TABLE 3

Standard care regimen

	Weeks 1 to 4		Procedure (Week 4)	Re-epithelialization to Week 8		Weeks 8 to 14	
	AM	**PM**		**AM**	**PM**	**AM**	**PM**
Cetaphil wash	X	X		X	X	X	X
Neutrogena Moisturizing Sunscreen	X			X	X	X	
4% hydroquinone	X					X	
0.05% tretinoin		X					X

TABLE 4

Data Collection Schedule

	Visit 1 Baseline 30 Days Before OR	Visit 2 Day of Procedure	Visit 3 4 Days After OR	Visit 4 7 Days After OR	Visit 5 10 Days After OR	Visit 6 2 Weeks After OR	Visit 7 6 Weeks After OR	Visit 8 10 Weeks After OR
Photo	X	X	X	X	X	X	X	X
Survey	X	X				X	X	X
Photo Evaluation	X	X	X	X	X	X	X	X

* Re-epithelialization defined as “the disappearance of all crusting or scabs from the face, when the facial skin appears smooth and pink.”

TABLE 5

Median patient satisfaction scores after skin product use (Visit 8 data, 10 weeks after surgery)

	ONDS Group 18 patients	Control Group 19 patients	p value
Easy to use	5	5	0.393
Too time consuming	1	1	0.666
Instructions were clear	5	5	0.803
Products caused discomfort	1	1	0.661
1=Strongly Disagree, 2=Disagree, 3=Neutral, 4=Agree, 5=Strongly Agree			
Self-reported compliance with skin product regimen	1	1	0.556
1=Always, 2=Most of the Time, 3=Sometimes, 4=Not Very Often, 5=Never			

TABLE 6

Median erythema score by visit number

Visit Number	ONDS Group	Control Group	p value
2	1 (n=21)	0 (n=18)	p = .009
3	2 (n=16)	2 (n=14)	p = .405
4	2 (n=14)	2 (n=9)	p = .895
5	2 (n=13)	2 (n=8)	p = .319
6	2 (n=10)	2 (n=11)	p = .818
7	1 (n=11)	1 (n=11)	p = .104
8	1 (n=10)	1 (n=8)	p = .349

* Score range: 0-3 (none, mild, moderate, severe)

TABLE 7

Levels of Evidence for Therapeutic Studies

Level	Description of evidence
I	High-quality, multi-centered or single-centered, randomized controlled trial with adequate power; or systematic review of these studies
II	Lesser-quality, randomized controlled trial; prospective cohort study; or systematic review of these studies
III	Retrospective comparative study; case-control study; or systematic review of these studies
IV	Case series
V	Expert opinion; case report or clinical example; or evidence based on physiology, bench research or “first principles”