Iontophoresis

Number: 0229

Policy

*Please see amendment for Pennsylvania Medicaid at the end of this CPB.

I. Aetna considers iontophoresis medically necessary for any of the following indications:

A. Delivery of local anesthetic before emergent skin puncture or dermatological procedures to reduce pain associated with these procedures; or
B. Intractable, disabling primary focal hyperhidrosis (see CPB 0113 - Botulinum Toxin (../100_199/0113.html)) when all of the following are met:

- Member is unresponsive or unable to tolerate pharmacotherapy prescribed for excessive sweating (e.g., anti-cholinergics, beta-blockers, or benzodiazapines); and
- Significant disruption of professional and/or social life has occurred because of excessive sweating; and
- Topical aluminum chloride or other extra-strength anti-perspirants are ineffective or result in a severe rash; or

Policy History

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Review History

Definitions

Additional Information

Clinical Policy Bulletin Notes
C. Iontophoretic administration of fentanyl for patient-controlled analgesia of acute post-operative pain; or
D. Sweat test by pilocarpine iontophoresis for the diagnosis of cystic fibrosis.

II. Aetna considers the following uses of iontophoresis experimental and investigational because of insufficient evidence of its effectiveness (not an all-inclusive list):

- Administration of acetic acid for treating rotator cuff disease (e.g., calcific tendinitis, rotator cuff tendinitis, and subacromial impingement syndrome)
- Administration of acetic acid and corticosteroid for treating epicondylitis
- Administration of acetylcholine and sodium nitroprusside for assessing risk of development and progression of cardiovascular disease
- Administration of non-steroidal anti-inflammatory drugs or corticosteroids for treating musculo-skeletal disorders (e.g., adhesive capsulitis (frozen shoulder), carpal tunnel syndrome, medial tibial stress syndrome, neck pain, patella-femoral pain syndrome, and patellar tendinopathy; not an all-inclusive list) Administration of sodium nitroprusside for treating systemic sclerosis
- Administration of treprostinil for treating diabetic ulcers
- Administration of tretinoin for treating atrophic scarring
- Administration of verapamil for treating Peyronie's disease
- Administration of vitamin C for treating melasma

See also CPB 0504 - Hyperhydrosis (../500_599/0504.html)

**Background**

Iontophoresis is the introduction of ionizable drugs through intact skin by the administration of continuous, direct electrical current into the tissues of the body. The sweat test by pilocarpine iontophoresis is the only practical and reliable laboratory test for confirmation of the diagnosis of cystic
fibrosis (CF). Localized sweating is stimulated pharmacologically, the amount of sweat is measured, and sodium and chloride levels determined. In patients with a suggestive clinical picture or a positive family history of CF, a chloride concentration greater than 60 mEq/L confirms the diagnosis.

Iontophoresis can be tried for intractable disabling primary hyperhidrosis when anti-perspirants or pharmacotherapy are not effective. Iontophoresis has been reported to provide relief in cases of primary hyperhidrosis of the hands and feet. A specialized electrode can be used to apply iontophoresis to the axillae. The procedure is repeated regularly, initially in 20-min sessions several times a week, gradually stretching out the interval between treatments to 1 to 2 weeks. The Drionic® device (General Medical Co., Los Angeles, CA) is an iontophoretic device that can be purchased for home use.

Walling and Swick (2011) noted that most cases of hyperhidrosis involve areas of high eccrine density, particularly the axillae, palms, and soles, and less often the cranio-facial area. Multiple therapies are available for the treatment of hyperhidrosis. Options include topical medications (most commonly aluminum chloride), iontophoresis, botulinum toxin injections, systemic medications (including glycopyrrolate and clonidine), and surgery (most commonly endoscopic thoracic sympathectomy [ETS]). These investigators reviewed the literature on the subject, with a focus on new and emerging treatment options. For axillary and palmo-plantar hyperhidrosis, topical treatment is recommended as first-line treatment. For axillary hyperhidrosis, botulinum toxin injections are recommended as 2nd-line treatment, oral medications as 3rd-line treatment, local surgery as 4th-line treatment, and ETS as 5th-line treatment. For palmar and plantar hyperhidrosis, the authors considered a trial of oral medications (glycopyrrolate 1 to 2 mg once- or twice-daily preferred to clonidine 0.1 mg twice-daily) as 2nd-line therapy due to the low cost, convenience, and emerging literature supporting their excellent safety and reasonable efficacy. Iontophoresis is
considered 3rd-line therapy for palmo-plantar hyperhidrosis; efficacy is high although so are the initial levels of cost and inconvenience. Botulinum toxin injections are considered 4th-line treatment for palmo-plantar hyperhidrosis; efficacy is high though the treatment remains expensive, must be repeated every 3 to 6 months, and is associated with pain and/or anesthesia-related complications. Endoscopic thoracic sympathectomy is a 5th-line option for palmar hyperhidrosis but is not recommended for plantar hyperhidrosis due to anatomic risks. For cranio-facial hyperhidrosis, oral medications (either glycopyrrolate or clonidine) are considered 1st-line therapy. Topical medications or botulinum toxin injections may be useful in some cases and ETS is an option for severe cranio-facial hyperhidrosis.

There is insufficient evidence that iontophoresis of corticosteroids is effective in treating musculoskeletal disorders. Hasson et al (1992) evaluated the pain alleviating effect of dexamethasone iontophoresis on delayed onset muscle soreness (DOMS) produced via an eccentric exercise bout, and to determine the effect on muscle function. Baseline data were collected on 18 female subjects for maximum isometric knee extension contraction (MVC), knee extension peak torque (PT), knee extension work (W), and muscle soreness perception (SP). All values were subsequently reassessed 24 and 48 hours after a 10-min bout of bench stepping. Immediately following the 24-hr re-assessment, the experimental (E) (n = 6) and placebo (P) (n = 6) groups received iontophoresis treatment while the control (C) group (n = 6) received no treatment. Percent deviation from baseline of SP was significantly less at 48 hours for the E group compared to P and C groups. However, MCV, PT, and W were no different between the 3 groups at 48 hours post muscle soreness bout. Moreover, this study evaluated an experimentally induced condition (DOMS), thus it has little bearing on clinical musculoskeletal disorders.

Schiffman and colleagues (1996) evaluated the short-term effect of iontophoretic delivery of dexamethasone (DEX) on the
signs and symptoms of temporomandibular disorders in patients who had concurrent temporomandibular joint disc displacement without reduction and capsulitis. A total of 27 patients with this clinical diagnosis were randomized to one of three groups: (i) treatment group (DEX and lidocaine hydrochloride); (ii) control group (lidocaine hydrochloride); and (iii) placebo group (pH-buffered saline). The authors reported that iontophoretic delivery of DEX and lidocaine was effective in improving mandibular function, but not in reducing pain, in temporomandibular disorders patients who had concurrent temporomandibular joint capsulitis and disc displacement without reduction.

In a pilot study, Li et al (1996) examined the effectiveness of DEX iontophoresis for the treatment of rheumatoid arthritis (RA) of the knee. A total of 10 subjects with RA were randomly assigned to either the experimental or placebo group. Iontophoresis treatments were given to both groups on days 1, 3, and 5. Five subjects in the experimental group received a mixture of 1 ml of DEX (4 mg/ml) and 1 ml of injectable sterile water; those in the placebo group received 2 ml of saline solution. Pain on movement, at rest, and on pressure, active joint count, and active range of motion, were evaluated on days 1, 5, and 20. The results suggested that DEX iontophoresis is more effective than placebo in relieving pain at rest and on movement in the RA knee. The finding of this small study needs to be verified by studies with larger sample size and longer follow-ups.

Gudeman and co-workers (1997) investigated whether iontophoresis of DEX in conjunction with other traditional modalities provides more immediate pain relief than traditional modalities alone. Forty affected feet were randomly assigned to one of two groups. In Group I, feet were treated with traditional modalities and placebo iontophoresis. In Group II, feet received the traditional modalities plus iontophoresis of dexamethasone. Both groups were treated 6 times over a 2-week period. The authors reported that although traditional modalities alone are ultimately effective, iontophoresis in
conjunction with traditional modalities provides immediate reduction in symptoms.

Most studies of iontophoresis for other indications are not well-designed. The studies have small sample sizes, lack appropriate control groups, and usually do not have objective outcome measures. As a result, it is still unclear whether iontophoresis (of a certain drug/agent) is clinically effective or that iontophoresis of the drug/agent is more effective than other forms of treatment. More research, especially randomized, controlled studies with large sample sizes and sound statistical analysis, is needed to ascertain the effectiveness of iontophoresis for the treatment of such conditions as temporomandibular joint disorders, musculo-skeletal/soft tissue injuries, herpes labialis, and post-herpetic neuralgia.

Baskurt et al (2003) reported that iontophoresis and phonophoresis of naproxen are equally effective electrotherapy methods in the treatment of lateral epicondylitis (n = 61 patients). The main drawback of this study is the lack of a placebo control group. Furthermore, the findings of this study are confounded by the fact that both groups were treated by other physiotherapy methods such as cold pack, progressive strengthening and stretching exercises. Thus, it is unclear whether the improvement is due to iontophoresis/phonophoresis or other physiotherapy methods.

Neeter and colleagues (2003) evaluated the effects of iontophoresis with DEX (n = 14) to iontophoresis with saline solution (n = 11) on patients who had acute (less than 3 months) pain from the Achilles tendon, in terms of range of motion, muscular endurance, pain and symptoms. Patients were evaluated before and after 2 weeks of treatment with iontophoresis, as well as after 6 weeks, 3 and 6 months and 1 year. Both groups then followed the same rehabilitation program for 10 weeks. Good reliability was found for the toe-raise and range of motion tests. Poor reliability was, however, found for the pain on palpation test, which was
excluded. No difference was found between or within groups for the toe-raise test. Several significant improvements were seen in the experiment group but not in the control group, in the range of motion test, pain during and after physical activity, pain during walking and walking up and down stairs, morning stiffness and tendon swelling. These investigators concluded that iontophoresis with DEX were found to have a positive effect in the treatment of patients with acute Achilles tendon pain. This was a small study (n = 25), albeit it a randomized one. The small sample size limited the possibilities to draw definite conclusions from the present findings.

Nirschl et al (2003) studied the effects of iontophoretic administration of DEX in controlling pain in patients with medial or lateral elbow epicondylitis. A total of 199 patients with elbow epicondylitis received 40 mA-minutes of either active or placebo treatment. Dexamethasone produced a significant 23-mm improvement on the 100-mm patient visual analog scale (VAS) ratings, compared with 14 mm for placebo at 2 days and 24 mm compared with 19 mm at 1 month. More patients treated with DEX than those treated with placebo scored moderate or better on the investigator's global improvement scale (52 % versus 33 %) at 2 days, but the difference was not significant at 1 month (54 % versus 49 %). Investigator-rated pain and tenderness scores favored DEX over placebo at 2 days. Patients completing 6 treatments in 10 days or less had better results than those treated over a longer period. The authors concluded that iontophoresis treatment was well-tolerated by most patients and was effective in reducing symptoms of epicondylitis at short-term follow-up. There appears to be little difference in VAS rating at 1 month between the 2 groups which corresponded with the investigator's global improvement scale (54 % versus 49 %). Thus, iontophoretic administration of DEX does not appear to have any long-term effect on elbow epicondylitis.

In a Cochrane review, Kroeling et al (2005) stated that no definitive statements on iontophoresis or other types of electrotherapy for mechanical neck disorders can be made.
The current evidence on iontophoresis, galvanic current (direct or pulsed), transcutaneous electrical nerve stimulation, electronic muscle stimulation, low- or high-frequency pulsed electromagnetic stimulation, and permanent magnets is lacking, limited, or conflicting. Possible new trials on these interventions should have larger patient samples and include more precise standardization and description of all treatment characteristics.

The BlueCross BlueShield Association Technology Evaluation Center (TEC) assessment of iontophoresis for medical indications (BCBSA, 2003) concluded that iontophoretic administration of non-steroidal anti-inflammatory drugs (NSAIDs) or corticosteroids for musculo-skeletal inflammatory disorders does not meet the TEC criteria. The TEC assessment found that randomized controlled clinical studies have not consistently found better outcomes from corticosteroids delivered by iontophoresis compared to placebo iontophoresis. In addition, the TEC assessment found no randomized controlled clinical studies comparing iontophoresis of NSAIDs and corticosteroids to these drugs delivered by another route, which is the comparison essential to this assessment. The TEC assessment explained: "In order to demonstrate the effectiveness of iontophoresis for drug delivery, there must be adequate evidence on both of the following questions: whether the effects of iontophoresis exceed placebo effects; and how iontophoretic drug delivery compares with alternative treatments, usually other routes of drug administration (e.g., topical, oral, injection). Evidence showing iontophoresis of an active drug to be superior to iontophoresis of placebo is necessary, but not sufficient. The crucial issue to this assessment is whether iontophoretic drug delivery is at least as beneficial as other treatments."

Osborne and Allison (2006) determined if, in the short-term, acetic acid and DEX iontophoresis combined with LowDye (low-Dye) taping are effective in treating the symptoms of plantar fasciitis. A total of 31 patients with medial calcaneal origin plantar fasciitis were recruited from 3 sports medicine
clinics. All subjects received 6 treatments of iontophoresis to the site of maximum tenderness on the plantar aspect of the foot over a 2-week period, continuous LowDye taping during this time, and instructions on stretching exercises for the gastrocnemius/soleus. They received 0.4 % DEX, placebo (0.9 % NaCl), or 5 % acetic acid. Stiffness and pain were recorded at the initial session, the end of 6 treatment sessions, and the follow-up at 4 weeks. Data for 42 feet from 31 subjects were used in the study. After the treatment phase, all groups showed significant improvements in morning pain, average pain, and morning stiffness. However for morning pain, the acetic acid/taping group showed a significantly greater improvement than the DEX/taping intervention. At the follow-up, the treatment effect of acetic acid/taping and DEX/taping remained significant for symptoms of pain. In contrast, only acetic acid maintained treatment effect for stiffness symptoms compared with placebo ($p = 0.031$) and DEX. The authors concluded that 6 treatments of acetic acid iontophoresis combined with taping gave greater relief from stiffness symptoms than, and equivalent relief from pain symptoms to, treatment with DEX/taping. For the best clinical results at 4 weeks, taping combined with acetic acid is the preferred treatment option compared with taping combined with DEX or saline iontophoresis.

There are several drawbacks with the findings of this study: (i) small sample size ($n = 31$), (ii) no long-term follow-up (patients were only followed for 4 weeks), and (iii) all groups showed significant improvements in morning pain, average pain, and morning stiffness -- i.e., placebo (saline) iontophoresis (plus taping) is effective in reducing pain and stiffness. It is also interesting to note that in a randomized controlled study ($n = 92$), Radford et al (2006) reported that LowDye taping (by itself) provided improvement in heel pain.

Brown et al (2006) stated that various strategies have emerged over recent years to enhance transdermal drug delivery, and these can be categorized into passive and active methods. The passive approach entails the optimization of formulation or
drug carrying vehicle to increase skin permeability. Passive methods, however do not greatly improve the permeation of drugs with molecular weights greater than 500 Da. In contrast active methods that normally involve physical or mechanical methods of enhancing delivery have been shown to be generally superior. Improved delivery has been shown for drugs of differing lipophilicity and molecular weight including proteins, peptides, and oligonucleotides using electrical methods (iontophoresis, electroporation), mechanical (abrasion, ablation, perforation), and other energy-related techniques such as ultrasound and needless injection. However, for these novel delivery methods to succeed and compete with those already on the market, the prime issues that require consideration include device design and safety, efficacy, ease of handling, and cost-effectiveness.

Andres and Murrell (2008) performed a systematic review to determine the best treatment options for tendinopathy. These researchers evaluated the effectiveness of NSAIDS, corticosteroid injections, exercise-based physical therapy, physical therapy modalities, shock wave therapy, sclerotherapy, nitric oxide patches, surgery, growth factors, and stem cell treatment. Corticosteroid injection and NSAIDS appear to provide pain relief in the short-term, but their effectiveness in the long-term has not been demonstrated. These researchers identified inconsistent results with shock wave therapy and physical therapy modalities (e.g., ultrasound, iontophoresis and low-level laser therapy). Current data support the use of eccentric strengthening protocols, sclerotherapy, and nitric oxide patches, but larger, multi-center trials are needed to confirm the early results with these treatments. Preliminary work with growth factors and stem cells is promising, but further study is needed in these fields. Surgery remains the last option due to the morbidity and inconsistent outcomes. The ideal treatment for tendinopathy remains unclear.

Amirjani et al (2009) examined the effectiveness of DEX iontophoresis as a non-invasive method of treating tunnel syndrome (CTS). These investigators performed a double-blind
randomized controlled trial comparing 6 sessions of iontophoresis with 0.4 % DEX sodium phosphate with distilled water in 17 patients. Outcome measures including nerve conduction studies, the Levine Self-Assessment Questionnaire, and the Semmes-Weinstein Monofilaments were done monthly for 6 months after intervention. Most of the outcome measures did not show any significant change following treatment. Although there was subjective improvement of symptom severity scores in the treatment group as quantified by the Levine Self-Assessment Questionnaire, similar improvement was also observed in the control group (p < 0.05). Although DEX iontophoresis is feasible in clinical settings and is well-tolerated by patients, iontophoresis of 0.4 % DEX was not effective in the treatment of mild-to-moderate CTS.

The University of Michigan Health System's clinical guideline on acute low back pain (2010) stated that iontophoresis is one of the interventions considered but not routinely recommended for the management of patients with acute low back pain. Furthermore, the Work Loss Data Institute's guideline on carpal tunnel syndrome (2011) noted that iontophoresis/phonophoresis are interventions/procedures that are under study and are not specifically recommended.

Well-designed studies (randomized controlled trials with large sample size and long-term follow-up) are needed to ascertain the clinical value of iontophoresis in the treatment of musculo-skeletal disorders.

There is insufficient evidence to support the use of verapamil iontophoresis for the treatment of patients with Peyronie's disease. Cabello Benavente and colleagues (2005) assessed the effects of transdermal iontophoresis with verapamil and DEX in patients with Peyronie's disease of less than 1 year of evolution. These researchers had treated 10 patients twice a week during 6 consecutive weeks using iontophoresis with a Miniphysionizer dispositive. This device generates a 2 mA electric current during 20 mins, which triggers the transdermal penetration of medication. In every session, DEX (8 mg) and
verapamil (5 mg) were administered inside a small self-adhesive receptacle on the penile skin overlying the fibrosis plaque. To evaluate the efficacy, penile curvature was measured by Kelami's test, while the plaque size was assessed by penile ultrasound. Other parameters like pain, erectile function and ability for vaginal intercourse were recorded using questionnaires. Safety parameters were also assessed during treatment. No improvement or progression in penile curvature was evidenced in any of the patients. The hardness of the plaque was reduced in 5 patients, becoming impalpable in 2 of them. Decrease in plaque volume was observed by penile ultrasound in 6. Pain improved in 8 patients, disappearing in 6 of them. One patient recovered his erectile function at the end of the treatment; whereas 3 referred that their ability for intercourse enhanced while 2 reported that treatment improved their sexual life in general. These investigators did not record any significantly side effects, except for a transitory and slight dermal redness on the site of electrode placement. The authors concluded that transdermal iontophoresis is an effective treatment for pain control in early stages of Peyronie's disease. Efficacy in reducing penile curvature seems to be limited. They noted that controlled clinical trials are needed to obtain more relevant clinical effects.

Greenfield et al (2007) performed a double-blind, placebo controlled trial to determine the effectiveness of verapamil delivered through electromotive drug administration. A total of 42 men with Peyronie's disease volunteered to participate in this study, which was approved by our institutional review board. A genito-urinary examination was performed on all patients, including plaque location, stretched penile length, objective measurement of curvature after papaverine injection and duplex ultrasound. Each subject was randomized to receive 10 mg verapamil in 4 cc saline or 4 cc saline via electromotive drug administration. A Mini-Physionizer (Physion, Mirandola, Italy) device was used at a power of 2.4 mA for 20 mins. Treatments were performed 2 times weekly for 3 months. After 3 months each patient was re-evaluated with physical examination and duplex ultrasound by a technician blinded to
the treatment received. A modified erectile dysfunction index of treatment satisfaction questionnaire was also completed by each patient. A total of 23 patients were randomized to the verapamil treatment group (group 1) and 19 were randomized to the saline group (group 2). There were no significant differences between patient groups with respect to patient age, disease duration or pre-treatment curvature. In group 1, 15 patients (65%) had measured improvement (mean of 9.1 degrees, range of 5 to 30), 5 (22%) had no change and in 3 (13%) the condition worsened. In group 2, 11 patients (58%) had measured improvement (mean of 7.6 degrees, range of 5 to 30), 7 (37%) showed no change and in 1 (5%) the condition worsened. To better evaluate effectiveness the total number of patients experiencing significant improvement (20 degrees or greater) was calculated and compared. Seven patients (30%) in group 1 and 4 (21%) in group 2 achieved this criterion. Although a greater percentage of patients treated with verapamil had improved curvature, the results were not statistically significant. The authors concluded that although a greater percentage of patients treated with verapamil in their electromotive drug administration protocol had a measured decrease in curvature, the results were not statistically significant. Further research is needed to determine if electrical current may have a role in the treatment of Peyronie's disease as well as if verapamil delivered via electromotive drug administration may have a role as effective treatment.

Akin-Olugbade and Mulhall (2007) stated that there are a wide variety of medical treatments that are available to the practicing urologist, including oral agents, topical creams and gels with or without iontophoresis, intralesional injection therapy, radiation therapy, extracorporeal shockwave therapy, and laser therapy for the treatment of Peyronie's disease. Medical management of Peyronie's disease might be a valuable treatment option for this debilitating disorder, especially in the early symptomatic stages of the disease. Although no single modality has been demonstrated to have superior efficacy, intralesional therapy appears to confer some benefit. Multi-center, large-scale, randomized, controlled studies are needed
to fully establish the effectiveness of the available treatments.

Sasso et al (2007) noted that the etiopathogenesis of Peyronie's disease is not yet clearly understood, no medical therapy is fully effective, and surgery remains the gold standard in patients with severe deformity and/or erectile dysfunction.

Iontophoresis has been used for the delivery of local anesthetic before skin puncture or painful dermal procedures. An assessment by the BlueCross BlueShield Association Technology Evaluation Center (BCBSA, 2003) concluded that iontophoresis to administer local anesthetic before skin puncture or dermal procedures meets the TEC criteria. This use of iontophoresis is most useful in emergent situations, as iontophoresis results in more rapid dermal anesthesia than topical anesthetic agents. Topical anesthetic agents (e.g., lidocaine/prilocaine (EMLA) cream) take approximately 30 mins to achieve maximal effect, and are sufficient for dermal anesthesia in non-emergent situations.

Turner and colleagues (2008) noted that effective assessment of endothelial function is an important tool for ascertaining individuals at risk of development and progression of cardiovascular disease. As an alternative to invasive tests of endothelial function, several non-invasive methods have been developed such as the use of laser Doppler flowmetry to measure cutaneous perfusion accompanied by iontophoresis of acetylcholine and sodium nitroprusside. It is evident from published reports that this approach not only provides a validated and reproducible method for evaluating and monitoring of endothelial function in patients with various pathological conditions, it may also be employed to examine disease progression and responsiveness to treatment; thus facilitating clinical trials. Moreover, a standardization of protocols would aid to reduce the apparent controversy observed in the literature. With its increasing use by other groups, it is anticipated that further published studies will help to provide a better understanding of the development and progression of cardiovascular disease.
There is evidence that a fentanyl iontophoretic transdermal system is an adequate substitute for intravenous patient controlled analgesia with morphine for acute post-operative pain. Pennington et al (2009) evaluated patients' assessment of fentanyl iontophoretic transdermal system (ITS) and morphine intravenous patient-controlled analgesia (IV PCA) convenience on 7 different subscales, using a validated patient ease of care (EOC) questionnaire in 2 prospective, open-label, randomized, phase IIIb clinical trials. Patients received fentanyl ITS or morphine IV PCA (n = 1,305) for up to 72 hrs after total hip replacement surgery (THR study) or abdominal or pelvic surgery (APS study). For the majority of items on the patient EOC questionnaire, trends suggested that greater percentages of patients reported the most positive response for fentanyl ITS than they did for morphine IV PCA in both studies; differences were particularly noteworthy for items on the Movement subscale. In the THR study, more patients in the fentanyl ITS group were responders compared with those in the morphine IV PCA group for the subscales Confidence with Device, Pain Control, Knowledge/Understanding, and Satisfaction. In the APS study, responder rates for these subscales did not differ between treatment groups. These findings indicated that patients assessed the EOC associated with fentanyl ITS higher compared with morphine IV PCA for the management of acute post-operative pain and suggested that fentanyl ITS has the potential to improve acute post-operative pain care for patients and nurses.

A pooled analysis of randomized controlled trials found fentanyl ITS was as safe and effective and more convenient than morphine PCA for acute post-operative pain. In this analysis of pooled data, Viscusi et al (2007) compared the safety and efficacy of the fentanyl ITS with morphine IV PCA from 3 multicenter, randomized, active-controlled trials (n = 1,941). Comparable percentages of patients reported success on the 24-hr patient global assessment of the method of pain control (fentanyl ITS, 80.5 %; morphine IV PCA, 81.0 %; difference = -0.5 %; 95 % confidence interval [CI]: -4.0 % to 3.0 %). Mean last pain intensity scores in the first 24 hours were comparable.
(fentanyl ITS, 3.1; morphine IV PCA, 3.0; difference = 0.07; 95% CI: -0.14 to 0.29). Relative dosing ratios of fentanyl to morphine overall and in subpopulations (age, BMI) were comparable over 6, 12, and 24 hours. The authors found that fentanyl ITS was equally effective when compared with morphine IV PCA for patient subpopulations (age, surgery type, and BMI). Discontinuation rates and the incidence of adverse events were similar between groups.

Poon et al (2009) reported on a meta-analysis of 2 placebo-controlled and 4 active-controlled randomized trials of fentanyl ITS. The authors found that fentanyl ITS was superior to placebo for post-operative analgesia using withdrawal secondary to inadequate analgesia and pain scores as outcome measures. Fentanyl ITS was found to be equivalent to morphine PCA when Patient Global Assessment was used as primary outcome measure. However, the authors found that there were significantly more patients in the fentanyl ITS group who withdrew due to inadequate analgesia. The authors suggested that this may be related to the pharmacokinetic profile of fentanyl ITS. The authors reported that the adverse effect and safety profile of fentanyl ITS seemed favorable. They concluded that fentanyl ITS is a promising novel modality for post-operative analgesia that is superior to placebo but may not be equivalent to morphine PCA as claimed by individual trials and recent reviews.

In a Cochrane review, Rajaratnam et al (2010) evaluated interventions used in the management of all types of melasma: epidermal, dermal, and mixed. Randomized controlled trials that examined topical and systemic interventions for melasma were included in this review. Study selection, assessment of methodological quality, data extraction, and analysis was carried out by 2 authors independently. These reviewers included 20 studies with a total of 2,125 participants covering 23 different treatments. Statistical pooling of the data was not possible due to the heterogeneity of treatments. Each study involved a different set of interventions. They can be grouped into those including a bleaching agent such as hydroquinone,
triple-combination creams (hydroquinone, tretinoin, and fluocinolone acetonide), and combination therapies (hydroquinone cream and glycolic acid peels), as well as less conventional therapies including rucinol, vitamin C iontophoresis, and skin-lightening complexes like Thiospot and Gigawhite. Triple-combination cream was significantly more effective at lightening melasma than hydroquinone alone (risk ratio [RR] 1.58, 95 % CI: 1.26 to 1.97) or when compared to the dual combinations of tretinoin and hydroquinone (RR 2.75, 95 % CI: 1.59 to 4.74), tretinoin and fluocinolone acetonide (RR 14.00, 95 % CI: 4.43 to 44.25), or hydroquinone and fluocinolone acetonide (RR 10.50, 95 % CI: 3.85 to 28.60). Azelaic acid (20 %) was significantly more effective than 2 % hydroquinone (RR 1.25, 95 % CI: 1.06 to 1.48) at lightening melasma but not when compared to 4 % hydroquinone (RR 1.11, 95 % CI: 0.94 to 1.32). In 2 studies where tretinoin was compared to placebo, participants rated their melasma as significantly improved in one (RR 13, 95 % CI: 1.88 to 89.74) but not the other. In both studies by other objective measures tretinoin treatment significantly reduced the severity of melasma. Thiospot was more effective than placebo (SMD -2.61, 95 % CI: -3.76 to -1.47). The adverse events most commonly reported were mild and transient such as skin irritation, itching, burning, and stinging. The authors concluded that the quality of studies evaluating melasma treatments was generally poor and available treatments inadequate. They stated that high-quality randomized controlled trials on well-defined participants with long-term outcomes to determine the duration of response are needed.

Lake and Wofford (2011) noted that patella-femoral pain syndrome (PFPS) is a common orthopedic condition for which operative and non-operative treatments have been used. Therapeutic modalities have been recommended for the treatment of patients with PFPS-including cold, ultrasound, phonophoresis, iontophoresis, neuromuscular electrical stimulation, electro-stimulation for pain control, electromyographic (EMG) biofeedback, and laser. These investigators determined the effectiveness of therapeutic modalities for the
treatment of patients with PFPS. In May and August 2010, Medline was searched using the following databases: PubMed, CINAHL, Web of Science Citation Index, Science Direct, ProQuest Nursing & Allied Health, and Your Journals@OVID. Selected studies were randomized controlled trials that used a therapeutic modality to treat patients with PFPS. The review included articles with all outcome measures relevant for the PFPS patient: knee extension and flexion strength (isokinetic and isometric), patella-femoral pain assessment during activities of daily life, functional tests (e.g., squats), Kujala patella-femoral score, and EMG recording from knee flexors and extensors and quadriceps femoris cross-sectional areas. Authors conducted independent quality appraisals of studies using the PEDro Scale and a system designed for analysis of studies on interventions for patella-femoral pain. A total of 12 studies met criteria: 1 on the effects of cold and ultrasound together, ice alone, iontophoresis, and phonophoresis; 3, neuromuscular electrical stimulation; 4, EMG biofeedback; 3, electro-stimulation for control of pain; and 1, laser. Most studies were of low-to-moderate quality. Some reported that therapeutic modalities, when combined with other treatments, may be of some benefit for pain management or other symptoms. There was no consistent evidence of any beneficial effect when a therapeutic modality was used alone. Studies did not consistently provide added benefit to conventional physical therapy in the treatment of PFPS. The authors concluded that none of the therapeutic modalities reviewed has sound scientific justification for the treatment of PFPS when used alone.

The European Association of Urology’s guidelines on penile curvature (Wespes et al, 2012) states that iontophoresis with verapamil 5 mg and dexamethasone 8 mg may improve penile curvature and plaque size (Level of evidence: 1b; Grade of recommendation: B).

An UpToDate review on “Epicondylitis (tennis and golf elbow)” (Jayanthi, 2012) states that “Studies of iontophoresis are small and preliminary, but the technique may provide some
short-term benefit. In one randomized controlled trial, patients treated with dexamethasone by iontophoresis noted significant improvement of symptoms at two days compared with placebo, but this benefit was lost at one month. Phonophoresis and iontophoresis with topical naproxen showed similar benefits in pain and function scores in patients with epicondylitis. No studies have compared topical NSAIDs with topical steroids in epicondylitis”.

Stefaniak et al (2012) stated that despite success of thoracic sympathectomy (ETS), there are patients that develop postoperatively intensive sweating of the trunk. The researchers presented outcomes of 3 of those methods: (i) removal of the clips, (ii) clipping of T6-T9, and (iii) regional abdomino-lumbar iontophoresis (RALI). Out of the group of 229 patients treated with ETS, there were 9 that requested removal of the clips, 3 were treated with T6-T9 video-thoracoscopic block, and 5 were treated with RALI. The intensity of the side effect has been evaluated subjectively (with overall and localized perception of intensity of sweating) and objectively (with gravimetry). The removal of the clips resulted in slow (about 12 months) diminishing of the intensity of sweating of the trunk; but the symptom did not disappear to the degree satisfactory for the patients. The T6-T9 block resulted in partial and transient diminishing of the symptom. The iontophoresis resulted in very promising short-term results. The authors concluded that removal of the clips from the sympathetic trunk did not provide resolution of compensatory sweating in 1 year of observation; T6-T9 block did not provide remedy for compensatory hyperhidrosis. Furthermore, they stated that regional abdomino-lumbar iontophoresis seems to be very promising, but further research and follow-up are mandatory.

In a systematic review, Winters et al (2013) evaluated the effectiveness of any intervention in the treatment of medial tibial stress syndrome (MTSS). Published or non-published studies, reporting randomized or non-randomized controlled trials (RCTs) of any treatment in subjects with MTSS were
eligible for inclusion. Treatments were assessed for effects on pain, time to recovery or global perceived effect. Computerized bibliographic databases (MEDLINE, CENTRAL, EMBASE, CINAHL, PEDro and SPORTDiscus) and trial registries were searched for relevant reports, from their inception to June 1, 2012. Grey literature was searched for additional relevant reports. The Cochrane Risk of Bias Tool was used to appraise study quality of RCTs whereas the Newcastle Ottawa Scale was used to appraise non-randomized trials. The “levels of evidence”, according to the Oxford Centre for Evidence-Based Medicine, addressed the impact of the assessed trials. Two reviewers independently performed the search for articles, study selection, data extraction and appraised methodological quality. A total of 11 trials were included in this systematic review. All RCTs revealed a high-risk of bias (Level 3 of evidence). Both non-RCTs were found to be of poor quality (Level 4 of evidence). Randomized controlled trials, studying the effect of a lower leg brace versus no lower leg brace, and iontophoresis versus phonophoresis, were pooled using a fixed-effects model. No significant differences were found for lower leg braces (standardized mean difference [SMD] -0.06; 95% CI: -0.44 to 0.32, p = 0.76), or iontophoresis (SMD 0.09; 95% CI: -0.50 to 0.68, p = 0.76). Iontophoresis, phonophoresis, ice massage, ultrasound therapy, periosteal pecking and extra-corporeal shockwave therapy (ESWT) could be effective in treating MTSS when compared with control (Level 3 to 4 of evidence). Low-energy laser treatment, stretching and strengthening exercises, sports compression stockings, lower leg braces and pulsed electromagnetic fields have not been proven to be effective in treating MTSS (level 3 of evidence). The authors concluded that none of the studies is sufficiently free from methodological bias to recommend any of the treatments investigated. Of those examined, ESWT appears to have the most promise.

In a Cochrane review, Kroeling et al (2013) evaluated the short-, intermediate- and long-term effects of electrotherapy on pain, function, disability, patient satisfaction, global perceived effect, and quality of life in adults with neck pain with and without radiculopathy or cervicogenic headache. These investigators
searched CENTRAL, MEDLINE, EMBASE, MANTIS, CINAHL, and ICL, without language restrictions, from their beginning to August 2012; they hand-searched relevant conference proceedings; and consulted content experts. Randomized controlled trials, in any language, investigating the effects of electrotherapy used primarily as uni-modal treatment for neck pain were selected for analysis. Quasi-RCTs and controlled clinical trials were excluded. These researchers used standard methodological procedures expected by the Cochrane Collaboration. These researchers were unable to statistically pool any of the results, but they assessed the quality of the evidence using an adapted GRADE approach. A total of 20 small trials (1,239 people with neck pain) containing 38 comparisons were included. Analysis was limited by trials of varied quality, heterogeneous treatment subtypes and conflicting results. The main findings for reduction of neck pain by treatment with electrotherapeutic modalities were as follows: (i) very low quality evidence determined that pulsed electromagnetic field therapy (PEMF) and repetitive magnetic stimulation (rMS) were more effective than placebo, while transcutaneous electrical nerve stimulation (TENS) showed inconsistent results; (ii) very low quality evidence determined that PEMF, rMS and TENS were more effective than placebo; (iii) low quality evidence (1 trial, 52 participants) determined that permanent magnets (necklace) were no more effective than placebo (standardized mean difference (SMD) 0.27, 95% CI: -0.27 to 0.82, random-effects model); (iv) very low quality evidence showed that modulated galvanic current, iontophoresis and electric muscle stimulation (EMS) were not more effective than placebo. There were 4 trials that reported on other outcomes such as function and global perceived effects, but none of the effects was of clinical importance. When TENS, iontophoresis and PEMF were compared to another treatment, very low quality evidence prevented the researchers from suggesting any recommendations. No adverse side effects were reported in any of the included studies. The authors concluded that they cannot make any definite statements on the effectiveness and clinical usefulness of electrotherapy modalities for neck pain. Since the evidence is
of low or very low quality, they were uncertain about the estimate of the effect. They stated that further research is very likely to change both the estimate of effect and their confidence in the results. Current evidence for PEMF, rMS, and TENS showed that these modalities might be more effective than placebo. When compared to other interventions the quality of evidence was very low thus preventing further recommendations. Funding bias should be considered, especially in PEMF studies. Galvanic current, iontophoresis, EMS, and a static magnetic field did not reduce pain or disability. These investigators stated that future trials on these interventions should have larger patient samples, include more precise standardization, and detail treatment characteristics.

Patel et al (2014) stated that atrophic scars cause significant patient morbidity. While there is evidence to guide treatment, there does not appear to be a systematic review to analyze the effectiveness of treatment options. To retrieve all evidence relating to atrophic scar treatment and evaluate using the Clinical Evidence GRADE score in order to allow clinicians to make evidence-based treatment choices. Searches were performed in Medline, EMBASE, CINHL and Cochrane to identify all English studies published evaluating treatment of atrophic scars on adults excluding journal letters. Each study was allocated a GRADE score based on type of study, quality, dose-response, consistency of results and significance of results. The end score allowed categorization of evidence into high, moderate, low or very low quality. A total of 41 studies were retrieved from searches including RCTs, observational studies, retrospective analyses and case reports of which 7% were allocated a high-quality score, 10% a moderate score, 7% a low score and 75% a very low score. Treatment modalities included ablative laser therapy, non-ablative laser therapy, autologous fat transfer, dermabrasion, chemical peels, injectables, subcision, tretinoin iontophoresis and combination therapy. The authors concluded that there is a paucity of good-quality clinical evidence evaluating treatment modalities for atrophic scarring. Evidence supports efficacy of laser, surgery and peel therapy. They stated that further
Biomolecular research is needed to identify targeted treatment options and more RCTs would make the evidence base for atrophic scar treatment more robust.

In a Cochrane review, Page et al (2014) synthesized the available evidence regarding the benefits and harms of electrotherapy modalities, delivered alone or in combination with other interventions, for the treatment of adhesive capsulitis (frozen shoulder). These investigators searched CENTRAL, MEDLINE, EMBASE, CINAHL Plus and the ClinicalTrials.gov and World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) clinical trials registries up to May 2014, unrestricted by language, and reviewed the reference lists of review articles and retrieved trials to identify any other potentially relevant trials. They included RCTs and controlled clinical trials using a quasi-randomized method of allocation that included adults with adhesive capsulitis and compared any electrotherapy modality to placebo, no treatment, a different electrotherapy modality, or any other intervention. The 2 main questions of the review focused on whether electrotherapy modalities are effective compared to placebo or no treatment, or if they are an effective adjunct to manual therapy or exercise (or both). The main outcomes of interest were participant-reported pain relief of 30% or greater, overall pain, function, global assessment of treatment success, active shoulder abduction, quality of life, and the number of participants experiencing any adverse event. Two review authors independently selected trials for inclusion, extracted the data, performed a risk of bias assessment, and assessed the quality of the body of evidence for the main outcomes using the GRADE approach. A total of 19 trials (1,249 participants) were included in the review. Four trials reported using an adequate method of allocation concealment and 6 trials blinded participants and personnel. Only 2 electrotherapy modalities (low-level laser therapy (LLLT) and pulsed electromagnetic field therapy (PEMF)) have been compared to placebo. No trial has compared an electrotherapy modality plus manual therapy and exercise to manual therapy and exercise alone. The 2 main questions of the review were
investigated in 9 trials. Low quality evidence from 1 trial (40 participants) indicated that LLLT for 6 days may result in improvement at 6 days. Eighty per cent (16/20) of participants reported treatment success with LLLT compared with 10% (2/20) of participants receiving placebo (risk ratio (RR) 8.00, 95% CI: 2.11 to 30.34; absolute risk difference 70%, 95% CI: 48% to 92%). No participants in either group reported adverse events. These researchers were uncertain whether PEMF for 2 weeks improved pain or function more than placebo at 2 weeks because of the very low quality evidence from 1 trial (32 participants). Seventy-five per cent (15/20) of participants reported pain relief of 30% or more with PEMF compared with 0% (0/12) of participants receiving placebo (RR 19.19, 95% CI: 1.25 to 294.21; absolute risk difference 75%, 95% CI: 53% to 97%). Fifty-five per cent (11/20) of participants reported total recovery of joint function with PEMF compared with 0% (0/12) of participants receiving placebo (RR 14.24, 95% CI: 0.91 to 221.75; absolute risk difference 55%, 95% CI: 31 to 79).

Moderate quality evidence from 1 trial (63 participants) indicated that LLLT plus exercise for 8 weeks probably results in greater improvement when measured at the 4th week of treatment, but a similar number of adverse events, compared with placebo plus exercise. The mean pain score at 4 weeks was 51 points with placebo plus exercise, while with LLLT plus exercise the mean pain score was 32 points on a 100-point scale (mean difference (MD) 19 points, 95% CI: 15 to 23; absolute risk difference 19%, 95% CI: 15% to 23%). The mean function impairment score was 48 points with placebo plus exercise, while with LLLT plus exercise the mean function impairment score was 36 points on a 100-point scale (MD 12 points, 95% CI: 6 to 18; absolute risk difference 12%, 95% CI: 6 to 18). Mean active abduction was 70 degrees with placebo plus exercise, while with LLLT plus exercise mean active abduction was 79 degrees (MD 9 degrees, 95% CI: 2 to 16; absolute risk difference 5%, 95% CI: 1% to 9%). No participants in either group reported adverse events. LLLT's benefits on function were maintained at 4 months. Based on very low quality evidence from 6 trials, these investigators were uncertain whether therapeutic ultrasound, PEMF, continuous
short wave diathermy, Iodex phonophoresis, a combination of Iodex iontophoresis with continuous short wave diathermy, or a combination of therapeutic ultrasound with transcutaneous electrical nerve stimulation (TENS) were effective adjuncts to exercise. Based on low or very low quality evidence from 12 trials, these researchers were uncertain whether a diverse range of electrotherapy modalities (delivered alone or in combination with manual therapy, exercise, or other active interventions) were more or less effective than other active interventions (e.g., glucocorticoid injection). The authors concluded that based upon low quality evidence from 1 trial, LLLT for 6 days may be more effective than placebo in terms of global treatment success at 6 days. Based upon moderate quality evidence from 1 trial, LLLT plus exercise for 8 weeks may be more effective than exercise alone in terms of pain up to 4 weeks, and function up to 4 months. It is unclear whether PEMF is more or less effective than placebo, or whether other electrotherapy modalities are an effective adjunct to exercise. They stated that further high quality RCTs are needed to establish the benefits and harms of physical therapy interventions (that comprise electrotherapy modalities, manual therapy and exercise, and are reflective of clinical practice) compared to interventions with evidence of benefit (e.g., glucocorticoid injection or arthrographic joint distension).

The Washington State Department of Labor and Industries’ guideline on “Work-related carpal tunnel syndrome diagnosis and treatment” (2014) stated that “The following treatments are not recommended for carpal tunnel syndrome because there is inadequate or conflicting evidence concerning their effectiveness: vitamin B6 (pyridoxine), oral diuretics, magnets, lasers, Botulinum toxin injections, iontophoresis”.

Sayegh and Strauch (2015) noted that lateral epicondylitis is a painful tendinopathy for which several non-surgical treatment strategies are used. Superiority of these non-surgical treatments over non-treatment has not been definitively established. These investigators examined if non-surgical treatment of lateral epicondylitis compared with observation
only or placebo provides (i) better overall improvement, (ii) less need for escape interventions, (iii) better outcome scores, and (iv) improved grip strength at intermediate- to long-term follow-up. The English-language literature was searched using PubMed and the Cochrane Central Register of Controlled Trials. Randomized-controlled trials comparing any form of non-surgical treatment with either observation only or placebo at follow-up of at least 6 months were included. Non-surgical treatments included injections (corticosteroid, platelet-rich plasma, autologous blood, sodium hyaluronate, or glycosaminoglycan polysulphate), physiotherapy, shock wave therapy, laser, ultrasound, corticosteroid iontophoresis, topical glyceryl trinitrate, or oral naproxen. Methodological quality was assessed with the Consolidated Standards of Reporting Trials (CONSORT) check-list, and 22 RCTs containing 2,280 patients were included. Pooled analyses were performed to evaluate overall improvement; requirement for escape interventions (treatment of any kind, outside consultation, and surgery); outcome scores (Patient-Rated Tennis Elbow Evaluation [PRTEE]; DASH; Pain-Free Function Index [PFFI]; EuroQoL [EQ]-5D; and overall function); and maximum and pain-free grip strength. Sensitivity analyses were performed using only trials of excellent or good quality. Heterogeneity analyses were performed, and funnel plots were constructed to assess for publication bias. Non-surgical treatment was not favored over non-treatment based on overall improvement (risk ratio [RR] = 1.05 [0.96 to 1.15]; p = 0.32), need for escape treatment (RR = 1.50 [0.84 to 2.70]; p = 0.17), PRTEE scores (mean difference [MD] = 1.47, [0.68 to 2.26]; p < 0.001), DASH scores (MD = -2.69, [-15.80 to 10.42]; p = 0.69), PFFI scores (standardized mean difference [SMD] = 0.25, [-0.32 to 0.81]; p = 0.39), overall function using change-from-baseline data (SMD = 0.11, [-0.14 to 0.36]; p = 0.37) and final data (SMD = -0.16, [-0.79 to 0.47]; p = 0.61), EQ-5D scores (SMD = 0.08, [-0.52 to 0.67]; p = 0.80), maximum grip strength using change-from-baseline data (SMD = 0.12, [-0.11 to 0.35]; p = 0.31) and final data (SMD = 4.37, [-0.65 to 9.38]; p = 0.09), and pain-free grip strength using change-from-baseline data (SMD = -0.20, [-0.84 to 0.43]; p = 0.53) and final data (SMD = -0.03, [-0.61 to
The authors concluded that pooled data from RCTs indicated a lack of intermediate- to long-term clinical benefit after non-surgical treatment of lateral epicondylitis compared with observation only or placebo.

Non-Steroidal Anti-Inflammatory Drugs or Corticosteroids for the Treatment of Patellar Tendinopathy:

In a RCT, Rigby and colleagues (2015) determined the differences among 2 iontophoretic drug-delivery systems (wireless patch versus wired dose controller) and a sham treatment in treating patellar tendinopathy. A total of 31 participants diagnosed with patellar tendinopathy (men = 22, women = 9, age = 24.5 ± 5.9 years) were included in this study. Participants were randomly assigned into 1 of 3 treatment groups: (i) wireless patch, (ii) wired dose controller, or (iii) sham treatment. Participants in the active treatment groups received 6 80 mA/min iontophoretic treatments using 2 ml of 4% dexamethasone sodium phosphate. During each visit, clinical outcome measures were assessed and then the assigned treatment was applied. Clinical outcome measures were Kujala Anterior Knee Pain Scale, pressure sensitivity, knee-extension force, and sit-to-stand pain assessment using a numeric rating scale. For each clinical outcome measure, these researchers used a repeated-measures analysis of co-variance to determine differences among the treatment groups over the treatment period. Participants reported a clinically important improvement on the Kujala Anterior Knee Pain Scale across all treatment groups, with no differences among groups (p = 0.571). A placebo effect was observed with pressure sensitivity (p = 0.0152); however, the active treatment decreased participants’ pain during the sit-to-stand test (p = 0.042). The authors concluded that a placebo effect occurred with the sham treatment group. Generally, improvement was noted in all groups regardless of treatment type, but greater pain reduction during a functional task was evident within the active treatment groups during the sit-to-stand test.

Sodium Nitroprusside for the Treatment of Systemic Sclerosis:
Little and associates (2015) examined the influence of dose of iontophoretic sodium nitroprusside as a first step in exploring a possible new therapeutic approach for systemic sclerosis (SSc). A total of 10 patients with SSc and 9 healthy controls were recruited. Blood flow in a single finger was assessed using laser Doppler imaging following iontophoresis of sodium nitroprusside at “doses” of 2, 1, 0.5 and 0 %. Graphs of perfusion over time (30 minutes) were produced for each dose; and from these curves, summary measures of response were calculated (area under curve [AUC]/baseline and maximum perfusion/baseline). These measures were subject to regression analysis to investigate the effect of dose on response and to consider whether response differed between patients and healthy controls. Individual responses to altering the dose of iontophoresed sodium nitroprusside were highly variable but there was evidence to suggest increased response at doses of 1.5 and 1 % (but not at 2 %) compared to 0 % for both AUC/baseline (p = 0.028 and p = 0.011, respectively) and maximum perfusion/baseline (p = 0.001 and p = 0.002, respectively). The authors stated that there was no evidence that responses differed between patients and controls.

Treprostinil for the Treatment of Diabetic Ulcers:

Hellmann et al (2015) examined if iontophoresis of treprostinil increases skin microvascular blood flux in the malleolus area of healthy subjects and diabetic patients. These researchers recruited 12 healthy subjects and 12 type II diabetic patients. Cathodal iontophoresis (40 mC/cm²) of treprostinil 250 µM and saline 0.9 % was performed in the malleolus area. Skin hyperemia was quantified using non-invasive laser speckle contrast imaging, and expressed as the AUC of cutaneous vascular conductance (CVC). In healthy controls and diabetic patients, treprostinil 250 µM induced a significant increase in CVC compared with saline (for diabetic patients, AUC 0 to 6 hours was 1,9970 ± 8,697; versus 2,893 ± 5,481 % BL.min, respectively; p = 0.002). In both groups, the peak flux was obtained between 30 minutes and 1 hour after the end of treprostinil iontophoresis and flux remained higher than
baseline up to 6 hours after ending of iontophoresis. No significant side-effect occurred. Cutaneous iontophoresis of 250 µM treprostinil increased microvascular blood flux in the malleolus area in healthy volunteers and diabetic patients, without inducing systemic or local side-effects. The authors concluded that treprostinil cathodal iontophoresis should be further investigated as a new local therapy for diabetic ulcers.

**Administration of Acetic Acid for Treating Rotator Cuff Disease:**

In a Cochrane review, Page and colleagues (2016) synthesized available evidence regarding the benefits and harms of electrotherapy modalities for the treatment of people with rotator cuff disease. These investigators searched the Cochrane Central Register of Controlled Trials (CENTRAL; 2015, Issue 3), Ovid Medline (January 1966 to March 2015), Ovid Embase (January 1980 to March 2015), CINAHL Plus (EBSCOhost, January 1937 to March 2015), ClinicalTrials.gov and the WHO ICTRP clinical trials registries up to March 2015, unrestricted by language, and reviewed the reference lists of review articles and retrieved trials, to identify potentially relevant trials. They included RCT and quasi-randomized trials, including adults with rotator cuff disease (e.g., calcific tendinitis, rotator cuff tendinitis, and subacromial impingement syndrome), and comparing any electrotherapy modality with placebo, no intervention, a different electrotherapy modality or any other intervention (e.g., glucocorticoid injection). Trials investigating whether electrotherapy modalities were more effective than placebo or no treatment, or were an effective addition to another physical therapy intervention (e.g., manual therapy or exercise) were the main comparisons of interest. Main outcomes of interest were overall pain, function, pain on motion, patient-reported global assessment of treatment success, quality of life (QOL) and the number of participants experiencing adverse events (AEs). Two review authors independently selected trials for inclusion, extracted the data, performed a risk of bias assessment and assessed the quality of the body of evidence for the main outcomes using the GRADE approach. These researchers included 47 trials (2,388
participants). Most trials (n = 43) included participants with rotator cuff disease without calcification (4 trials included people with calcific tendinitis); 16 (34 %) trials investigated the effect of an electrotherapy modality delivered in isolation. Only 23 % were rated at low-risk of allocation bias, and 49 % were rated at low-risk of both performance and detection bias (for self-reported outcomes). The trials were heterogeneous in terms of population, intervention and comparator, so none of the data could be combined in a meta-analysis. In 1 trial (61 participants; low-quality evidence), pulsed therapeutic ultrasound (3 to 5 times a week for 6 weeks) was compared with placebo (inactive ultrasound therapy) for calcific tendinitis. At 6 weeks, the mean reduction in overall pain with placebo was -6.3 points on a 52-point scale, and -14.9 points with ultrasound (MD -8.60 points, 95 % CI: -13.48 to -3.72 points; absolute risk difference 17 %, 7 % to 26 % more). Mean improvement in function with placebo was 3.7 points on a 100-point scale, and 17.8 points with ultrasound (mean difference (MD) 14.10 points, 95 % CI: 5.39 to 22.81 points; absolute risk difference 14 %, 5 % to 23 % more); 91 % (29/32) of participants reported treatment success with ultrasound compared with 52 % (15/29) of participants receiving placebo (RR 1.75, 95 % CI: 1.21 to 2.53; absolute risk difference 39 %, 18 % to 60 % more). Mean improvement in QOL with placebo was 0.40 points on a 10-point scale, and 2.60 points with ultrasound (MD 2.20 points, 95 % CI: 0.91 points to 3.49 points; absolute risk difference 22 %, 9 % to 35 % more). Between-group differences were not important at 9 months. No participant reported AEs. Therapeutic ultrasound produced no clinically important additional benefits when combined with other physical therapy interventions (8 clinically heterogeneous trials, low-quality evidence). The authors were uncertain whether there were differences in patient-important outcomes between ultrasound and other active interventions (manual therapy, acupuncture, glucocorticoid injection, glucocorticoid injection plus oral tolmetin sodium, or exercise) because the quality of evidence was very low. Two placebo-controlled trials reported results favoring LLLT up to 3 weeks (low-quality evidence), however combining LLLT with other physical therapy
interventions produced few additional benefits (10 clinically heterogeneous trials, low-quality evidence). These investigators were uncertain whether TENS was more or less effective than glucocorticoid injection with respect to pain, function, global treatment success and active range of motion (ROM) because of the very low-quality evidence from a single trial. In other single, small trials, no clinically important benefits of PEMF, microcurrent electrical stimulation (MENS), acetic acid iontophoresis, and microwave diathermy were observed (low- or very low-quality evidence). No AEs of therapeutic ultrasound, LLLT, TENS or microwave diathermy were reported by any participants; AEs were not measured in any trials investigating the effects of PEMF, MENS or acetic acid iontophoresis. The authors concluded that based on low-quality evidence, therapeutic ultrasound may have short-term benefits over placebo in people with calcific tendinitis, and LLLT may have short-term benefits over placebo in people with rotator cuff disease. They stated that further high quality placebo-controlled trials are needed to confirm these results. In contrast, based on low-quality evidence, PEMF may not provide clinically relevant benefits over placebo, and therapeutic ultrasound, LLLT and PEMF may not provide additional benefits when combined with other physical therapy interventions. These investigators were uncertain whether TENS was superior to placebo, and whether any electrotherapy modality provided benefits over other active interventions (e.g., glucocorticoid injection) because of the very low-quality of the evidence. They stated that further trials of electrotherapy modalities for rotator cuff disease should be based upon a strong rationale and consideration of whether or not they would alter the conclusions of this review.

**Iontophoresis for Plantar Hyperhidrosis:**

Singh and colleagues (2016) evaluated current literature regarding the management of plantar hyperhidrosis in the form of a structured review. These investigators performed a literature search using various databases and search criteria. The literature reported the use of conservative, medical and
surgical treatment modalities for the management of plantar hyperhidrosis. However, long-term follow-up data are rare and some treatment modalities currently available are not fully understood. The authors concluded that there is a considerable dearth in the literature on the management of plantar hyperhidrosis. They stated that further study in larger populations with longer follow-up times is needed to evaluate the long-term effects of treatment. Moreover, they noted that iontophoresis, botulinum toxin injection and lumbar sympathectomy are promising treatment modalities for this disorder.

**Transepithelial Corneal Collagen Cross-Linking by Iontophoresis for Keratoconus:**

In a prospective, non-randomized study, Lin and colleagues (2015) evaluated the early clinical results of keratoconic eyes treated with transepithelial iontophoresis corneal collagen cross-linking (I-CXL) within 1 year. A total of 23 eyes of 23 patients with progressive keratoconus with minimum corneal thickness from 380 µm to 420 µm (including the epithelium) were included in this study and treated with i-CXL. Scoring of pain and foreign body sensation, slit lamp examination, uncorrected visual acuity (UCVA) and best corrected distance visual acuity (BCVA), corneal topography, anterior segment optical coherence tomography (AS-OCT), in-vivo corneal confocal microscopy and endothelial cell count were assessed before surgery and at 1, 3, 6 and 12 months post-operatively. Paired t-test was applied for statistical analysis. Moderate pain and foreign body sensation were reported by most patients on post-operative day 1, but rapidly decreased and eventually disappeared on day 3. Mild epithelial damage was observed on day 1, and the epithelium fully recovered on day 3. Improvement of UCVA and BCVA were recorded at 3 months and 12 months post-operatively. Orbscan II corneal topography revealed the significant reductions of Kmax and Kmin from 3 months to 12 months (Kmax, t = 2.912, p < 0.01, Kmin, t = 2.508, p < 0.05) post-operatively while the other parameters remained stable. The Kmax and Kmin at 12 months were 52.94
± 4.87 and 46.78 ± 3.71, respectively, while the pre-operative values were 54.37 ± 5.56 and 48.53 ± 3.57, respectively. Within 1 month post-operatively, AS-OCT exhibited an increase of reflectance with a white line (demarcation line) in the anterior stroma, in-vivo confocal microscopy also showed the significant thickening and increased connections of collagen fibers with maximal depth of about 133 µm. The corneal endothelial cell density remained stable (t = 0.915, p > 0.05). None of the patients showed post-operative complications such as corneal infection, scarring, ulcer, persistent epithelial defect, etc. The authors concluded that preliminary clinical results within 1 year post-operatively demonstrated the safety and effectiveness of I-CXL for the management of progressive keratoconus. This technique was applicable for keratoconic eyes with minimum corneal thickness around 400 µm. They stated that I-CXL showed the advantage of short time consuming in surgery, rapid recovery and few complication, and has the potential to become a valid alternative for the treatment of keratoconus.

In a Cochrane review, Sykakis and co-workers (2015) examined if there is evidence that CXL is a safe and effective treatment for halting the progression of keratoconus compared to no treatment. These investigators searched the Cochrane Central Register of Controlled Trials (CENTRAL; 2014, Issue 7), Ovid Medline, Ovid Medline In-Process and Other Non-Indexed Citations, Ovid Medline Daily, Ovid OLDMedline (January 1946 to August 2014), Embase (January 1980 to August 2014), Latin American and Caribbean Health Sciences Literature Database (LILACS) (1982 to August 2014), Cumulative Index to Nursing and Allied Health Literature (CINAHL) (1982 to August 2014), OpenGrey (System for Information on Grey Literature in Europe) (www.opengrey.eu/), the metaRegister of Controlled Trials (mRCT) (www.controlled-trials.com), ClinicalTrials.gov (www.clinicaltrials.gov) and the World Health Organization International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en). These researchers used no date or language restrictions in the electronic searches for trials. They last searched the electronic databases on August 28, 2014. They included RCTs where CXL with UVA light and
riboflavin was used to treat people with keratoconus and was compared to no treatment. Two review authors independently screened the search results, assessed trial quality, and extracted data using standard methodological procedures expected by Cochrane. The primary outcomes were 2 indicators of progression at 12 months: (i) increase in maximum keratometry of 1.5 diopters (D) or more and (ii) deterioration in UCVA of more than 0.2 logMAR. These researchers included 3 RCTs conducted in Australia, the United Kingdom, and the United States that enrolled a total of 225 eyes and analyzed 219 eyes. The total number of people enrolled was not clear in 2 of the studies. Only adults were enrolled into these studies. Out of the eyes analyzed, 119 had CXL (all using the epithelium-off technique) and 100 served as controls. One of these studies only reported comparative data on review outcomes. All 3 studies were at high-risk for performance bias (lack of masking), detection bias (only 1 trial attempted to mask outcome assessment), and attrition bias (incomplete follow-up). It was not possible to pool data due to differences in measuring and reporting outcomes. The authors identified a further 3 unpublished trials that potentially had enrolled a total of 195 participants. There was limited evidence on the risk of progression. Analysis of the first few participants followed-up to 1 year in 1 study suggested that eyes given CXL were less likely to have an increase in maximum keratometry of 1.5 D or more at 12 months compared to eyes given no treatment, but the CI were wide and compatible with no effect or more progression in the CXL group (RR 0.12, 95 % CI: 0.01 to 2.00, 19 eyes). The same study reported the number of eyes with an increase of 2 D or more at 36 months in the whole cohort with a RR of 0.03 favoring CXL (95 % CI: 0.00 to 0.43, 94 eyes). Another study reported "progression" at 18 months using a different definition; people receiving CXL were less likely to progress, but again the effect was uncertain (RR 0.14, 95 % CI: 0.01 to 2.61, 44 eyes). These researchers judged this to be very low-quality evidence due to the risk of bias of included studies, imprecision, indirectness and publication bias but noted that the size of the potential effect was large. On average, treated eyes had a less steep cornea (approximately 2 D less steep) (MD
-1.92, 95 % CI: -2.54 to -1.30, 94 eyes, 1 RCT, very low-quality evidence) and better UCVA (approximately 2 lines or 10 letters better) (MD -0.20, 95 % CI: -0.31 to -0.09, 94 eyes, 1 RCT, very low-quality evidence) at 12 months. None of the studies reported loss of 0.2 logMAR acuity. The data on corneal thickness were inconsistent. There were no data available on QOL or costs. Adverse events (AEs) were not uncommon but mostly transient and of low clinical significance. In 1 trial, 3 out of 12 participants treated with CXL had an AE including corneal edema, anterior chamber inflammation, and recurrent corneal erosions. In 1 trial at 3 years, 3 out of 50 participants experienced AEs including mild diffuse corneal edema and para-central infiltrate, peripheral corneal vascularization, and sub-epithelial infiltrates and anterior chamber inflammation. No AEs were reported in the control groups. The authors concluded that evidence for the use of CXL in the management of keratoconus is limited due the lack of properly conducted RCTs.

Jouve and associates (2017) compared the safety, effectiveness, and microstructural corneal changes during 2 years after conventional corneal collagen cross-linking (C-CXL) and I-CXL for keratoconus. A total of 80 eyes of 80 patients with progressive keratoconus were treated by C-CXL (n = 40) or I-CXL (n = 40). Patients were investigated before surgery and 1, 3, 6, 12, and 24 months after treatment. These researchers measured central corneal thickness and maximal simulated keratometry values (Kmax) and performed specular microscopy and in-vivo confocal microscopy at each time-point. The demarcation line was assessed 1 month after treatment. Kmax remained stable after I-CXL during the entire study period (p = 0.56), whereas the average keratometry increased by 0.2 diopter (50.9 ± 5.6 to 51.1 ± 5.2). Kmax significantly decreased 1 (p = 0.02) to 2 years (p < 0.01) after C-CXL, with an average decrease of 1.1 diopters (49.9 ± 4.5 to 48.8 ± 4.2). The failure rate of I-CXL was 20 % and that of C-CXL 7.5 %. The demarcation line was superficially visible in 35 % of cases after I-CXL compared with 95 % of cases after C-CXL. Endothelial cell density and central corneal thickness remained stable during the entire study period. The
change in Kmax 2 years after C-CXL and I-CXL and the pre-operative Kmax were negatively correlated (r = 0.14, p = 0.013, and r = 0.17, p = 0.007, respectively). The authors concluded that I-CXL halted progression of keratoconus less efficiently than did C-CXL after 2 years of follow-up. Moreover, they stated that longer prospective studies are still needed to ensure the effectiveness of I-CXL.

<table>
<thead>
<tr>
<th>CPT Codes / HCPCS Codes / ICD-10 Codes</th>
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<td><strong>Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by &quot;+&quot;:</strong></td>
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<td><strong>CPT codes covered if selection criteria are met:</strong></td>
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<td>97033</td>
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<td><strong>HCPCS codes not covered for indications listed in the CPB:</strong></td>
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<td><strong>ICD-10 codes covered if selection criteria are met:</strong></td>
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<td>G89.18</td>
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<td>L74.510 - L74.519</td>
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<td>R61</td>
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<td><strong>ICD-10 codes not covered for indications listed in the CPB (not all-inclusive):</strong></td>
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**Sweat Test by Pilocarpine Iontophoresis:**

**CPT codes covered if selection criteria are met:**

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**ICD-10 codes covered if selection criteria are met:**

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<th>Description</th>
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<tr>
<td>E84.0 - E84.9</td>
<td>Cystic fibrosis</td>
</tr>
</tbody>
</table>
The above policy is based on the following references:


55. Viscusi ER, Siccardi M, Damaraju CV, et al. The safety and


66. Stefaniak T, Cwigon M, Laski D. In the search for the


87. Rigby JH, Mortensen BB, Draper DO. Wireless versus


AETNA BETTER HEALTH® OF PENNSYLVANIA

Amendment to
Aetna Clinical Policy Bulletin Number:
CPB 0229 – Iontophoresis

There are no amendments for Medicaid.

www.aetnabetterhealth.com/pennsylvania
Updated 04/26/2017