Title: Alcohol Injection Therapy for Morton's Neuroma

Populations
- Individuals: With Morton's neuroma

Interventions
- Interventions of interest are:
  - Intrallesional alcohol injection(s)

Comparators
- Comparators of interest are:
  - Conservative therapy (eg, rest, metatarsal supports)
  - Surgical excision

Outcomes
- Relevant outcomes include:
  - Symptoms
  - Resource utilization
  - Treatment-related morbidity

DESCRIPTION
Morton's neuroma is a common and painful compression neuropathy of the dorsal foot that may be referred to by other names, including intermetatarsal neuroma, interdigital neuroma, interdigital neuritis, and interdigital/Morton's metatarsalgia. Historically,
Morton's neuroma has been treated with conservative measures, surgery, or minimally invasive procedures. Alcohol injection is a minimally invasive alternative to open surgery to treat Morton's neuroma. Alcohol technically is a sclerosant that causes chemical neurolysis through dehydration, necrosis and precipitation of the treated area, ultimately destroying the lesion after multiple injections.

**OBJECTIVE**

The objective of this policy is to evaluate the net health outcome when alcohol injections are used to treat Morton's neuroma compared with surgery or other conservative therapy.

**BACKGROUND**

**Neuroma**

A neuroma is a growth or tumor consisting of nerve tissue that develops as part of a normal reparative process following nerve injury. Neuromas may develop after injury to a nerve or as a result of chronic irritation, pressure, stretch, poor repair of nerve lesions or previous neuromas, laceration, crush injury, or blunt trauma.1 Neuromas typically appear about 6 to 10 weeks after trauma with most presenting within 1 to 12 months after injury or surgery. They may gradually enlarge over a period of 2 to 3 years and may or may not be painful. Pain from a neuroma may be secondary to traction on the nerve by scar tissue, compression of the sensitive nerve endings by adjacent soft tissues, ischemia of the nervous tissue or ectopic foci of ion channels that elicit neuropathic pain. Patients may describe the pain as a low-intensity dull pain or intense paroxysmal burning pain, often triggered by external stimuli such as touch or temperature. Neuroma formation has been implicated as a contributor of neuropathic pain in residual limb pain, postthoracotomy, postmastectomy, and postherniorrhaphy pain syndromes. They may coexist with phantom pain or can predispose to it.

**Morton's Neuroma**

Morton's neuroma is a common and painful compression neuropathy of the common digital nerve of the foot that may be referred to by other names, including interdigital neuroma, interdigital neuritis, and interdigital or Morton's metatarsalgia.1-3 It is histologically characterized by perineural fibrosis, endoneurial edema, axonal degeneration and local vascular proliferation. Thus, some investigators do not consider Morton's neuroma to be a true neuroma; instead, they consider it to be an entrapment neuropathy that occurs secondary to compression of the common digital nerve under the overlying transverse metatarsal ligament. The incidence and prevalence of Morton's neuroma are not clear, but it appears 10-fold more often in women than in men with an average age at presentation of around 50 years.4

The pain associated with Morton's neuroma is usually a throbbing, burning or shooting pain that is localized to the plantar aspect of the foot. It is typically located between the 3rd and 4th metatarsal heads although it may appear in other close-by locations.1,2 The pain may radiate to the toes and can be associated with paresthesia. The pain can be
severe, and the condition may become debilitating to the extent that patients are apprehensive and anxious about walking or touching their foot to the ground. It is aggravated by walking in shoes with a narrow toe box or high heels that cause excessive pronation and excessive forefoot pressure; removal of tight shoes typically relieves the pain.

Diagnosis of Morton's Neuroma
Although a host of imaging methods may be used to aid diagnosis of Morton's neuroma, including plain radiographs, magnetic resonance imaging, and ultrasonography, objective findings are unique to this condition and are primarily used to establish a clinical diagnosis. Thus, a patient's toes often show splaying or divergence. Patients may describe the feeling of a “lump” on the foot bottom or a feeling of walking on a rolled-up or wrinkled sock. Clinical examination with medial and lateral compression may reproduce the painful symptoms with a palpable “click” on interspace compression (Mulder sign).

Treatment of Morton's Neuroma
Management of patients with a diagnosis of Morton's neuroma typically proceeds through a pathway that starts with conservative approaches, such as the use of metatarsal pads in shoes, and orthotic devices that alter supination and pronation of the affected foot. These approaches are aimed at reducing pressure and irritation of the affected nerve. They may provide some relief, but do not alter the underlying pathology. There is scant evidence to support the effectiveness or comparative effectiveness of these practices. In 1 case series, investigators evaluated a 3-stage protocol of “stepped care” through which private practice patients (N=115) advanced from stage I (education plus footwear modifications, and a metatarsal pad) to stage II (steroid injections with local anesthetic or local anesthetic alone), into stage III (surgical resection) if stages I and II did not bring relief within 3 months. Overall, 97 of 115 patients (85%) believed that they had improved with the treatment program. However, twenty-four patients (21%) eventually required surgical excision of the nerve and 23 of those (96%) had satisfactory results.

Surgical Techniques: Historically, surgical intervention is considered the definitive therapy. The most common procedure is open excision of the interdigital nerve pathology through a dorsal or plantar approach. A second procedure referred to as nerve decompression with neurolysis or translocation of the affected part of the interdigital nerve has been used to treat Morton's neuroma. Although this approach uses smaller incisions and seems to have more rapid recovery than open excision of the neuroma, it is reported to be a more demanding procedure that requires specialist training and equipment and is less common in practice. No randomized clinical trials have been reported which compared the effectiveness of different management approaches for Morton's neuroma.

A Cochrane systematic review that was originally published in 2004 showed insufficient evidence to assess the effectiveness of surgical and non-surgical interventions for
Morton's neuroma. A more recent review published in 2013 summarized the results of surgical excision studies that included a total of 250 patients. In general, these series were poorly reported and highly heterogeneous, used disparate outcome measures, had short follow-up periods (average, 2-10 years) and could not be directly compared.

In the only prospective comparative study of surgical methods, the dorsal approach resulted in earlier weight bearing (mean, 16 days vs 23 days, respectively) and return to work (mean, 22 days vs 37 days, respectively) compared with a plantar approach in 52 total cases at average follow-up of 3 years. Painful scars were more common with the plantar approach \( (n=5) \) compared with the dorsal approach \( (n=2) \), with only 1 patient in each group experiencing a recurrence of symptoms. Other case series of primary neurectomy showed reduction of pain in more than 50% to 100% of patients, with self-reported satisfaction rates from 52% to 86%, at mean follow-up periods that ranged from 24 to 126 months. Common complications included paresthesia (51% to 82% reported), scar tenderness or hypersensitivity (6% to 32%), and wound infection (1.4% to 9.7%).

Long-term outcomes of surgical resection have been reported in 2 additional series that involved a total of 159 cases that were refractory to conservative management. One series \( (N=78) \) reported mean follow-up of 4.6 years (range, 0.8-8.1 years). With a dorsal approach, a total of 82% of patients with longstanding symptoms (mean duration, 33 months) reported excellent or good results, 10% had a fair result with restriction of activities or pain, while 8% had no improvement at all after surgery. Complications included wound infections in 8 cases that resolved with antibiotics, 5 had persistent hypersensitive scars, and 4 developed local keloid formations. Eight cases (10%) required revision due to neuroma recurrence at a mean of about 2 years after index surgery. The second long-term series \( (N=81) \) reported mean follow-up of 15.3 years (range, 10-20 years), the longest available in the literature. With a mostly dorsal approach (97% of cases), outcomes were reported excellent in 45%, good in 32% and fair in 15%; 8% reported poor results after surgery and were referred for revision. Paresthesia in the supplying area of the resected nerve was reported in 72% of cases, while normal sensation was reported in 26%. Other surgical complications were not reported in this series.

**Ablation Techniques:** Alternative approaches to treat refractory Morton's neuroma involves several minimally invasive procedures aimed at in situ destruction of the pathology, including intralesional alcohol injections. Dehydrated ethanol has been shown to inhibit nerve function in vitro, has high affinity for nerve tissue and causes direct damage to nerve cells via dehydration, cell necrosis, and precipitation of protoplasm, leading to neuritis and a pattern of Wallerian degeneration. Technically, ethanol is a sclerosant that causes chemical neurolysis of the nerve pathology, but is considered an ablative procedure for this policy. The use of ultrasound guidance during this procedure has been shown to increase surgical accuracy, improve outcomes, and shorten procedure duration.
Regulatory Status
Alcohol injection for Morton's neuroma is a surgical procedure and, as such, is not subject to regulation by the U.S. Food and Drug Administration.

POLICY
A. Clinical Indications for Percutaneous Alcohol (4-29% solution) Nerve Sclerosing (PANS) Injections
PANS injections are considered medically necessary for treatment of Morton's neuroma when all of the following conservative therapies, performed within 6 months of the initiation of PANS, have been attempted and have been documented as having failed:

1. Change in shoe types that are reported to result in neuroma-like symptoms
2. Change or limitation in activities that are reported to result in neuroma-like symptoms
3. Use of metatarsal pads (placed proximal to the metatarsal heads) to reduce pressure on the nerve by "spreading the metatarsals"
4. Cortisone injections administered 2 (minimum) to 3 times in a 6 week period (unless documented to be otherwise contraindicated)

PANS injections are expected to be performed according to the following protocol:

1. Two injections (CPT 64455 administered at 5-10 day intervals)
   Note: If the patient is unable to tolerate a second injection, PANS treatment would be terminated.
2. If there is a clinically significant positive response - symptoms reduced - reported and documented after 2 injections, up to 5 additional (or less if the patient reports elimination of neuroma symptoms) injections at 5-10 day intervals may be administered if symptoms persist.
3. If, however, two consecutive PANS injections fail to achieve continued and clinically significant symptom improvement, subsequent PANS injections would be considered not medically necessary and not reimbursed. Documentation failing to report interval status improvements prior to the administration of the next injection will be considered to be evidence of a lack of symptom improvement.

B. Clinical Indications for Percutaneous Alcohol (30-100% solution) Nerve Destruction (PAND) Injections
PAND injections (CPT 64632) are considered medically necessary for treatment of Morton's neuroma when all of the following conservative therapies, performed within 6 months of the initiation of PAND, have been attempted and have been documented as having failed:

1. Change in shoe types that are reported to result in neuroma-like symptoms
2. Change or limitation in activities that are reported to result in neuroma-like symptoms
3. Use of metatarsal pads (placed proximal to the metatarsal heads) to reduce pressure on the nerve by "spreading the metatarsals"

4. Cortisone injections administered 2 (minimum) to 3 times in a 6 week period (unless documented to be otherwise contraindicated)

5. A minimum of 2 percutaneous alcohol nerve sclerosing injections with no significant clinical improvement documented. Initiation of PAND injections would not be appropriate if PANS injections are not tolerated

PAND injections are expected to be performed according to the following protocol:
1. Ultrasonic or fluoroscopic imaging guidance (hard copy clear images must be recorded and available, upon request, for review)
   NOTE: The imaging guidance needle placement is considered part of the injection global fee and not separately reimbursed.

2. If there is a clinically significant positive response - symptoms reduced - reported and documented after 2 injections, up to 3 additional (or less if the patient reports elimination of neuroma symptoms) injections at 14 day intervals may be administered.

3. If, however, two consecutive PAND injections fail to achieve continued and clinically significant symptom improvement, subsequent PAND injections would be considered not medically necessary and not reimbursed. Documentation failing to report interval status improvements prior to the administration of the next injection will be considered to be evidence of a lack of symptom improvement.

C. PANS injections and PAND injections are considered **not medically necessary** when the above indications are not met.

**Policy Guidelines**
1. The medical record must adequately describe the patient's clinical state (history, physical findings, laboratory and other tests), eg, identification of the problem including diagnosis, precipitating events, quantity and quality of pain, test results, response to previous conservative treatment, as well as any other pertinent evaluation and management elements of the history, examination, and medical decision making.

2. The medical record must contain documentation indicating the reason for the procedure, the concentration of the alcohol solution injected, and a description of the procedure performed – including whether imaging guidance was used.

3. When a specific neuroma is injected, it will be considered one injection service regardless of the number of injections administered at that specific anatomical location on a single date of service.

4. The medical necessity for injections of more than two sites at one session is considered uncommon. Performance and submitting claims for such injections are likely to result in a request for medical records that must clearly document the medical necessity of these additional injections.
5. Failure of percutaneous alcohol nerve sclerosing (PANS) injections to achieve long term elimination or clinically significant reduction in symptoms precludes the medical necessity for repeated or continued PANS injections.

6. Failure of percutaneous alcohol nerve destruction (PAND) injections to achieve long term elimination or clinically significant reduction in symptoms precludes the medical necessity for repeated or continued PAND injections.

7. Payment for all substances injected is included in the amount paid for the injection and not separately reimbursable.

RATIONALE
This policy is based on a literature review of MEDLINE. The most recent update with literature review covered the period through April 25, 2017.

Assessment of efficacy for therapeutic intervention involves a determination of whether the intervention improves health outcomes. The optimal study design for this purpose is a randomized controlled trial (RCT) that includes clinically relevant measures of health outcomes.

For Morton's neuroma, relevant outcomes are pain, functional outcomes, and patient satisfaction. Because the outcomes are primarily subjective, evidence from RCTs with placebo controls is particularly important to assess the procedure's efficacy.

Intralesional Alcohol Injections for Morton's Neuroma
No RCTs or nonrandomized interventional trials were identified. Several case series have been published on the use of alcohol injections to treat Morton's neuroma. Summaries of these series appear in Table 1.

Treatment in all the case series consisted of injections of alcohol combined with an anesthetic (eg, lidocaine or bupivacaine). Injections were repeated at 2-week intervals, if symptoms persisted. On average, across studies, each patient received approximately 4 injections. Ultrasound guidance was used in all of the series described in Table 1. Outcomes were patient-reported and consisted of various measures of pain and satisfaction.

The largest series identified was reported by Pasquali et al (2015), who described a retrospective 2-center case series of 508 patients who received ultrasound-guided alcohol injection from 2001 to 2012 for Morton's neuroma.12 Eligible patients presented with 2nd or 3rd web space symptoms and had failed 3 months of conservative treatment with insoles and nonsteroidal anti-inflammatory drugs. Patients were injected with a 50% alcohol plus mepivacaine solution, with a mean of 3 injections (range, 1-4 injections) per neuroma. Pain at the Morton's neuroma site was assessed on a visual analog scale (VAS) ranging from 0 to 10, by local adverse reactions at 1 week postprocedure (0=no reaction; 1=minimal swelling, pain, redness; 2=significant swelling, pain redness), and patient-reported satisfaction. Pain scores improved from a mean preinjection VAS score of 8.7 to a mean postinjection score of 3.6 at 1 year (change in VAS score, p<0.001). At 1 year postinjection, 74.5% of patients were completely satisfied with the procedure. Fifty (9.3%) feet eventually required operative excision.
Table 1. Case Series of Intralesional Alcohol Injections for Morton's Neuroma

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>N</th>
<th>Treatment</th>
<th>Mean FU, mo</th>
<th>Results</th>
<th>Surgical FU, N (%)</th>
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</table>
| Perini et al (2016) | 220 | Alcohol, lidocaine | 19          | • Median NRS pain score improved from 9 to 3  
• 88.6% reported improved limitations of everyday activities  
• Reduction in neuropathic pain (100% to 45%)  
• No change in nociceptive pain (47% to 53%) | 14 (6%)             |
| Pasquali et al (2015) | 508 | Alcohol, mepivacaine | 12          | • Mean VAS pain score improved from 8.7 to 3.6  
• 74.5% completely satisfied | 50 (9%)             |
| Musson et al (2012) | 75  | Alcohol, bupivacaine | 14          | • Mean VAS pain score improved from 8.5 to 4.2  
• 32% complete symptom relief; 33% partial relief; 35% no relief | 17 (20%)            |
| Hughes et al (2007) | 101 | Alcohol, bupivacaine | 12          | • Mean VAS pain score improved from 8 to 0  
• 84% “essentially pain free”; 8% “mild/moderate pain”; 8% “no difference” | 3 (3%)              |
| Fanucci et al (2004) | 40  | Alcohol, carbocaine | 10          | • 21 completely satisfied; 9 satisfied with minor complications; 6 satisfied with major complications; 4 dissatisfied | 4 (10%)             |

FU: follow-up; NRS: numeric rating scale; VAS: visual analog scale.

Morgan et al (2014) reported on a systematic review that included the studies above published through February 2012 plus another by Dockery (1999) and compared the need for subsequent surgery after alcohol injections for Morton's neuroma with or without ultrasound guidance. Reviewers concluded that use of ultrasound guidance for alcohol injections to treat Morton's neuroma could reduce the need for subsequent surgery better than unguided treatments.

SUMMARY OF EVIDENCE

For individuals who have Morton's neuroma who receive intralesional alcohol injection(s), the evidence includes retrospective case series. Relevant outcomes are symptoms, resource utilization, and treatment-related morbidity. The body of evidence is weak, consisting of fewer than 10 case series reporting on treatment response of patients with refractory Morton's neuroma. The available series have generally reported that some patients experience pain relief and express satisfaction with the procedure. However, relief is not universally achieved. Some evidence has suggested that surgery after alcohol injections in failed cases is more complex and challenging than in untreated patients due to the presence of fibrosis. There is a lack of controlled trials comparing alcohol injections to alternative therapies and there are no controlled studies comparing outcomes for alcohol injections to those for surgery in patients who all are surgical candidates.

CLINICAL INPUT RECEIVED FROM PHYSICIAN SPECIALTY SOCIETIES AND ACADEMIC MEDICAL CENTERS

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests, input was received from 5 academic medical centers and 2 specialty societies while this policy was under review in 2015. Input was consistent that the use of alcohol injections to treat Morton's neuroma is investigational.
PRACTICE GUIDELINES AND POSITION STATEMENTS

American College of Foot and Ankle Surgeons

The American College of Foot and Ankle Surgeons released a clinical practice guideline (now referred to as a clinical consensus statement) in 2009 on the diagnosis and treatment of forefoot disorders. The consensus statement reports that 3 to 7 dilute alcohol injections of 4% alcohol injected at 5 to 10 day intervals has been associated with an 89% success rate with 82% of patients achieving complete relief of symptoms. The statement's pathway for treatment of intermetatarsal space neuroma lists decompression, excision, and cryogenic neuroablation under surgical management options.

Association of Extremity Nerve Surgeons

The Association of Extremity Nerve Surgeons issued 2014 Clinical Practice Guidelines in which they make the following conclusions regarding alcohol injections:

“The literature regarding alcohol injections is equivocal. There may be some short-term positive effect, but long-term effect is poor for this therapy. Some of the literature recommends using 30% alcohol solution to get effective results. However, there is not enough data to support the use of alcohol. As a general rule, we do not advocate the use of alcohol injections”

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS

Not applicable.

ONGOING AND UNPUBLISHED CLINICAL TRIALS

A search of ClinicalTrials.gov in May 2017 did not identify any ongoing or unpublished trials that would likely influence this policy.

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

CPT/HCPCS

For Percutaneous Alcohol Nerve Sclerosing (PANS) injections:
64455 Injection(s), anesthetic agent and/or steroid, plantar common digital nerve(s) (eg, Morton's neuroma)

For Percutaneous Alcohol Nerve Destruction (PAND) injections (Morton's neuroma):
64632 Destruction by neurolytic agent; plantar common digital nerve

ICD-9 Diagnoses

355.6 Lesion of plantar nerve (Morton's metatarsalgia, neuralgia, or neuroma)
**ICD-10 Diagnoses**

- **G57.61** Lesion of plantar nerve, right lower limb
- **G57.62** Lesion of plantar nerve, left lower limb
- **G57.63** Lesion of plantar nerve, bilateral lower limbs

**REVISIONS**

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**REFERENCES**


Other References
2. Blue Cross and Blue Shield of Kansas Podiatry Liaison Committee, January 2012; January 2013.