Cochrane Library

Cochrane Database of Systematic Reviews

Treatments for Morton's neuroma (Protocol)

Matthews BG, Thomson CE, McKinley JC, Harding MP, Ware RS

Matthews BG, Thomson CE, McKinley JC, Harding MP, Ware RS.
Treatments for Morton's neuroma (Protocol).
Cochrane Database of Systematic Reviews 2021, Issue 7. Art. No.: CD014687.
DOI: 10.1002/14651858.CD014687.

www.cochranelibrary.com

TABLE OF CONTENTS

[Intervention Protocol]

Treatments for Morton's neuroma

Barry G Matthews[1], Colin E Thomson[2], John C McKinley[3], Michael P Harding[4], Robert S Ware[5]

[1]Faculty of Health, School of Clinical Sciences, Queensland University of Technology (QUT), Brisbane, Australia. [2]Department of Trauma & Orthopaedics, The Royal Infirmary of Edinburgh and St John's Hospital Livingston, Edinburgh, UK. [3]Royal Infirmary of Edinburgh and Royal Hospital for Sick Children, Edinburgh, UK. [4]University of South Australia (City East), Adelaide, Australia. [5]Menzies Health Institute Queensland, Griffith University, Brisbane, Australia

Contact address: Barry G Matthews, barry@informpodiatry.com.au.

Editorial group: Cochrane Neuromuscular Group.
Publication status and date: New, published in Issue 7, 2021.

Citation: Matthews BG, Thomson CE, McKinley JC, Harding MP, Ware RS. Treatments for Morton's neuroma (Protocol). *Cochrane Database of Systematic Reviews* 2021, Issue 7. Art. No.: CD014687. DOI: 10.1002/14651858.CD014687.

ABSTRACT

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

To assess the benefits and harms of interventions for Morton's neuroma.

BACKGROUND

Description of the condition

Morton's neuroma presents as a painful neuropathy resulting from a benign enlargement of the common plantar digital nerve. This nerve condition most frequently presents in the third web space. When using the term web space, we are describing the fleshy area extending from the level of the intermetatarsophalangeal joint to the interdigital space. Strictly, the neuroma extends from the intermetatarsal space, distally to the interdigital space. Web spaces are numbered first to fourth (medial to lateral). The second most common presentation is in the second web space. It rarely presents in the first or fourth web spaces (Hughes 2007; Park 2018; Pasquali 2015; Seok 2016).

The precise aetiology of Morton's neuroma is poorly understood, with many proposed theories, including larger nerve size (Betts 1940), nerve ischaemia (constriction or obstruction of the blood flow to a nerve) (Nissen 1948), bursitis (inflammation of a fibrous sac that acts as a cushion between the metatarsal heads) (Bossley 1980), narrow web space (Levitsky 1993), and reduced ankle dorsiflexion (Barrett 2005). There is inconclusive evidence supporting theories of association between neuroma development and nerve size (Govsa 2005; Levitsky 1993), forefoot width and heel height in footwear (Matthews 2019), and narrow web space (Park 2017). Limited evidence of an association between Morton's neuroma and reduced ankle dorsiflexion has been reported (Naraghi 2016).

The common name for the condition, Morton's neuroma, is an eponym describing a benign growth of nerve tissue. The nerve changes were first described in 1835 by Italian anatomist, Filippo Civinini (Pasero 2006). European studies may use the eponym Civinini-Morton's to describe the condition (Samaila 2020). Lewis Durlacher first described the symptoms in 1845 (Durlacher 1845). In 1876, Thomas Morton, who believed the symptoms were caused by the fourth metatarsophalangeal joint, called the condition metatarsalgia. Morton's treatment for the condition was to surgically remove the joint and the adjacent soft tissue, which included the common plantar digital nerve (Morton 1876). The condition was first described as Morton's neuroma in 1958 (Larson 2005).

Since 2017, the US National Library of Medicine has mapped the term 'Morton neuroma' within the medical subject headings for indexing articles (NCBI 2021). While there are many eponyms and pathophysiological names for the condition (Larson 2005; Matthews 2019), Morton's neuroma is an accepted misnomer and has become the predominant term in recent times.

People with Morton's neuroma usually report burning or shooting pain located in the third or second web spaces, often with radiating paraesthesia (abnormal tingling or 'pins and needles' sensation) into the corresponding toes, or a clicking sensation in the forefoot. When weight bearing, people with Morton's neuroma often report the sensation of walking on a pebble, lump or stone (Dando 2017). In severe cases, the condition can impact on the person's mobility, ability to pursue activities, and quality of life (Thomson 2013). Morton's neuroma is the most common compressive neuropathy after carpal tunnel syndrome, affecting approximately 88 in every 100,000 women and 50 in every 100,000 men presenting for care by their General Practitioner in the UK (Latinovic 2006).

The diagnosis of Morton's neuroma can be challenging, with a range of presenting symptomatic and objective findings (Dando 2017), including tenderness or pain on palpation of the web space (Mahadevan 2015). Ultrasound has been proposed as a cost-effective and accurate method to confirm the diagnosis of Morton's neuroma, especially in cases where the clinical diagnosis is equivocal (Bignotti 2015), but a false diagnosis of asymptomatic web space nerve enlargements can occur when ultrasound is used without a clinical assessment (Symeonidis 2012).

Description of the intervention

The treatment goals for Morton's neuroma are to minimise pain and improve function. Interventions for Morton's neuroma may be nonsurgical or surgical (involving an incision). A common term used in both nonsurgical and surgical treatments is neurolysis, which has multiple meanings. Neurolysis may be defined as the destruction or dissolution of nerve tissue, or the surgical release of a nerve caught in an adhesion. To distinguish between these definitions, we have used the terms temperature neurolysis or chemical neurolysis for destruction of nerve tissue, and surgical neurolysis for surgical release of the nerve.

Nonsurgical interventions may be further divided into noninvasive (non-skin-penetrating) treatments and invasive (skin-penetrating) treatments. Nonsurgical noninvasive interventions reported to be used in clinical practice include various physical therapies, such as ultrasound, electrical stimulation, whirlpool, massage (Nunan 1997), and manipulation (Cashley 2015; Govender 2007); nonsteroidal anti-inflammatory drugs (Nunan 1997), orthoses (Gaynor 1989; Hirschberg 2000; Kilmartin 1994), and extracorporeal shockwave therapy (ESWT) (Seok 2016).

Although steroid injection is often the initial nonsurgical invasive treatment for Morton's neuroma, reports vary as to its effectiveness.

How the intervention might work

Interventions for the treatment of Morton's neuroma provide a diverse range of proposed therapeutic effects, but evidence in the peer-reviewed literature for many of these effects is limited. From a nonsurgical and noninvasive perspective, mobilisation or manipulation (Govender 2007), and footwear modification (Bennett 1995) are speculated to reduce pain by reducing web space compression. Foot orthoses may reduce plantar forefoot pressure (de Oliveira 2019), and ESWT may suppress nociceptive nerve fibres and result in pain reduction (Seok 2016).

From a nonsurgical invasive perspective, corticosteroid injections induce atrophy of the webspace tissue, possibly decreasing compression and inflammation of the nerve (Park 2018). Alcohol injections may induce neuritis and Wallerian nerve degeneration (chemical neurolysis) until the nerve is destroyed or completely ceases to function (Dockery 1999).

From a surgical perspective, nerve excision (neurectomy) is essentially amputation of the nerve or neuroma to alleviate chronic pain (Bucknall 2016). Surgical neurolysis aims to decompress the nerve to relieve pain whilst maintaining normal nerve function and toe sensation (Villas 2008). Metatarsal osteotomies may also decompress the nerve, relieving pain (Lee 2017).

Why it is important to do this review

The authors of the original Cochrane Review in 2004 found that there was an insufficient number of quality trials within the evidence base to reach firm conclusions about the effectiveness of surgical and nonsurgical interventions for Morton's neuroma (Thomson 2004). Seven subsequent 'systematic reviews' of varying quality considering a range of interventions for Morton's neuroma have been published since 2014. None has provided a comprehensive summary of the certainty of the evidence across the breadth of treatments from nonsurgical through to surgical interventions.

OBJECTIVES

To assess the benefits and harms of interventions for Morton's neuroma.

METHODS

Criteria for considering studies for this review

Types of studies

Study designs will include parallel-group trials and cross-over trials. The number of groups studied in each trial can be two or more. We will only include trials where allocation to intervention group is either randomised or quasi-randomised (that is, allocation using methods that are partly systematic, for example by alternation, use of a case record number, or date of attendance). We will include trials whether allocation occurs at the participant level (one participant with one Morton's neuroma) or at the cluster level (one participant with two or more Morton's neuromas receiving one or more interventions). We will include studies reported as full text, those published as abstract only, and unpublished data. There will be no restrictions as to language or date.

Types of participants

We will include study participants with a diagnosis of Morton's neuroma confirmed by one or more diagnostic criteria from each of the History, Physical examination and Confirmatory test categories described below.

History

- Pain located in the first, second, third, or fourth web space (Seok 2016).
- Paraesthesia, including pins and needles, shooting pains, or burning sensations in the forefoot or toe/s (Dando 2017).
- A weight bearing sensation of walking on pebbles, a lump or a stone (Dando 2017).
- Tight fitting (usually forefoot width) or high heel footwear aggravates symptoms (Dando 2017).

Physical examination

- Tenderness or pain with dorsal/plantar compression of the web space (Dando 2017; Mahadevan 2015).
- Mulder's sign/click/manoeuvre/test (palpable click felt with firm plantar pressure with thumb over suspected neuroma while compressing forefoot with other hand) (Dando 2017; Mahadevan 2015; Mulder 1951).

Confirmatory tests

- Ultrasound: 5 mm or greater transverse thickening of the plantar digital nerve at the web space that is well defined and grey in appearance (hypoechoic) (Dando 2017; Van Hul 2011).
- MRI: 5 mm or greater transverse thickening of the plantar digital nerve that appears to have the same signal intensity (isointense) relative to muscle tissue, which has a grey appearance on T1-weighted images, and less signal intensity (hypointense) relative to fat tissue, which has a white appearance on T2-weighted image (Van Hul 2011).
- Nerve conduction studies (Aydinlar 2014).
- Histological confirmation of excised tissue (Giakoumis 2013).

We will exclude participants with a history of the following comorbidities or characteristics.

- Local tissue injury or disease (e.g. metatarsophalangeal capsulitis, forefoot adventitial bursitis, stress fracture, schwannoma or mononeuropathies such as tarsal tunnel syndrome).
- Systemic conditions resulting in polyneuropathies (e.g. rheumatoid arthritis, multiple sclerosis, vitamin B_{12} deficiency, diabetes).
- Proximal neural defects (e.g. radiculopathy).

Where studies include a subset of relevant participants we will contact authors to obtain data for the subgroup of interest. If we cannot source subgroup data, we will include the study in the review but not in any meta-analysis.

Types of interventions

We will include trials that compare any surgical or nonsurgical intervention with any control, placebo, nonsurgical or surgical intervention. We will include studies with co-interventions when they are provided to each group equally. We will exclude trials that evaluate interventions following Morton's neuroma surgery.

We will group interventions into one of the following categories.

Nonsurgical treatments

- Noninvasive interventions (e.g. mobilisation/manipulation, footwear, metatarsal padding, ESWT or foot orthoses).
- Invasive interventions (e.g. corticosteroid, alcohol sclerosing or botulinum toxin injections, radiofrequency ablation or cryoneurolysis).

Surgical treatments

- Neurectomy (surgery on the Morton's neuroma with excision of the nerve).
- Surgical neurolysis (surgery on the Morton's neuroma without excision of the nerve).
- Osteotomy (surgery on the metatarsal adjacent to the Morton's neuroma).

Types of outcome measures

We will define time points for measuring primary and secondary outcomes as short term (less than three months from baseline), intermediate term (three months to less than 12 months from baseline), and long term (12 months or longer from baseline). If

more than one outcome occurs within a time interval, we will choose the outcome closest to three months (short term), six months (intermediate term) and 12 months (long term). Where trials use multiple measures to evaluate the same outcome (such as pain measured using different questionnaires), we will use pain reported on a 0 to 100 visual analogue scale (VAS) as the primary outcome measure. Where available, we will extract end point scores for our primary analysis.

The outcomes listed below are those of interest to the review. We will exclude studies that have not measured at least one of these outcomes and include studies that have measured one or more of these outcomes, even if no outcome data are available or reported.

Primary outcomes

- **Pain**

We will include VAS, numerical rating scales or pain scales (or subscales) of participant-reported outcome measures for use with foot or ankle diseases (Jia 2017). Where possible, we will express all similar continuous pain scales as a mean difference and any dissimilar scales as a standardised mean difference. When necessary, we will transform scales so that lower numerical rating corresponds to lower pain by reflecting the recorded pain score by the median value of the scale.

There are no published data investigating the minimal clinically important differences (MCID) for Morton's neuroma. Published randomised controlled trials (RCTs) have used a 15-point change (in Mahadevan 2016) and a 30-point change (in Lizano-Diez 2017) on a 0 to 100 pain VAS. A study investigating acute pain found that a difference of approximately 13 points (95% confidence interval (CI) 10 to 17) represented the minimum change that was clinically significant (Gallagher 2001). Based on these studies, we will use a 15-point change on a 0 to 100 pain VAS as the MCID.

Secondary outcomes

- **Function:** measured by self-report using questionnaire scales (e.g. Foot Function Index disability or activity subscales) or objective measures of functional capacity (e.g. six-minute walk test)
- **Satisfaction or health-related quality of life (HRQoL):** measured by self-report questionnaire (e.g. Johnson scale) (Johnson 1988)
- **Adverse events**
  - increase in pain: measured by self-report
  - unable to wear preferred footwear due to symptoms
  - any other emergent or intervention-related event, e.g. infection, hypoaesthesia (absent or reduced sensitivity to skin stimulation), callosities (hard, thickened skin) over plantar scars, or complex regional pain syndrome (McQuay 1997)

Search methods for identification of studies

Electronic searches

The Cochrane Neuromuscular Information Specialist will search the following databases.

- Cochrane Neuromuscular Specialised Register (until search date; Appendix 1).
- Cochrane Central Register of Controlled Trials (CENTRAL; until search date; Appendix 2).
- MEDLINE (1946 to search date; Appendix 3).
- Embase (1974 to search date; Appendix 4).
- Cumulative Index to Nursing and Allied Health Literature (CINAHL) Plus (1937 to search date; Appendix 5).

We will also conduct a search of clinical trials registries.

- US National Institutes for Health Clinical Trials Registry, ClinicalTrials.gov (www.ClinicalTrials.gov; Appendix 6).
- World Health Organization (WHO) International Clinical Trials Registry Portal (ICTRP; apps.who.int/trialsearch/; Appendix 7).

We will search all databases from their inception to the present, and we will impose no restriction on language of publication or age of study participant.

Searching other resources

We will search reference lists of all primary studies and review articles for additional references.

Data collection and analysis

Selection of studies

We will export search results into Covidence, where we will remove duplicates. Two review authors (BM and MH) will independently screen titles and abstracts of all the potential studies we identify as a result of the search for inclusion, and code them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. We will retrieve the full-text study reports/publications and two review authors (BM and MH) will independently screen the full text to identify studies for inclusion, and identify and record reasons for exclusion of the ineligible studies. We will resolve any disagreement through discussion or, if required, we will consult a third person (CT). We will identify and exclude duplicates and collate multiple reports of the same study so that each study rather than each report is the unit of interest in the review. We will record the selection process in sufficient detail to complete a PRISMA flow diagram and 'Characteristics of excluded studies' table.

Data extraction and management

We will use a data extraction form for study characteristics and outcome data, which we will pilot on at least one study in the review. Two review authors (BM and RW) will independently extract study characteristics from included studies. We will resolve disagreements by consensus or by involving a third person (CT). We will extract the following study characteristics: study design and setting, characteristics of participants (e.g. disease severity and age), eligibility criteria, intervention details, the outcomes assessed, source(s) of study funding, and any conflicts of interest among investigators. If participants have more than one neuroma (clustering), we will record the number of feet and the number of neuromas.

Two review authors (BM and RW) will independently extract outcome data from included studies. We will note in the 'Characteristics of included studies' table if trials did not report outcome data in a usable way. We will resolve disagreements by consensus or by involving a third person (CT). One review author (BM) will transfer data into RevMan Web 2021. A second review

author (RW) will check the outcome data entries and spot-check study characteristics for accuracy against the trial report.

We will convert categorical data to dichotomous data for measures of treatment effect with predetermined division points.

- For an odd number of categories, we will combine the response options favouring the intervention above the central category as one category and the remaining responses as the second category. For example, Bucknall 2016 has a statement 'The surgery has met my expectations' with the categorical responses 'strongly agree, agree, no opinion, disagree, or strongly disagree'. We would dichotomise this with 'strongly agree' and 'agree' in one category and the remaining responses as the other category.
- For an even number of categories, we will combine half the total response options favouring the intervention as one category and the remaining responses as the second category. For example, Akermark 2008 includes a question regarding scar tenderness, with the categorical responses 'none, slight, moderate, severe'. We would dichotomise this with 'none' and 'slight' in one category and 'moderate' and 'severe' as the other category.

When reports require translation, the translator will extract data directly using a data extraction form, or authors will extract data from the translation provided. Where possible, a review author will check numerical data in the translation against the study report.

We will use Covidence software to collect the data extracted from included studies.

Assessment of risk of bias in included studies

Two review authors (BM and JM) will independently assess risk of material bias for each result (as a minimum, those included in summary of findings tables) using the Cochrane Risk of bias 2 (RoB 2) criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Boutron 2019).

For trials with more than two intervention groups we will follow the additional guidance for assessing the risk of bias in Chapter 23 of the *Handbook* (Higgins 2019). We will resolve any disagreements by discussion or by involving another author (CT).

We will assess the risk of bias according to the following domains.

- Bias arising from the randomisation process.
- Bias due to deviations from intended interventions.
- Bias due to missing outcome data.
- Bias in measurement of the outcome.
- Bias in selection of the reported result.
- Bias arising from the timing of identification and recruitment of participants (for cluster-randomised trials only).

We will grade each potential source of bias as high, low, or some concerns and provide a justification for our judgement. We will report the source(s) of information for each decision using, for example, a quote from the study report. Where information on risk of bias relates to unpublished data or correspondence with a trialist, we will note this in the risk of bias table. We will summarise the risk of bias judgements across different studies for each of the domains listed. We will summarise the risk of bias for each key outcome (across domains) for each study and address risk of bias when synthesising results (see Data synthesis) (Boutron 2019).

When considering bias due to deviations from intended interventions, we will address the question of assignment rather than adherence to intervention.

We will use Covidence software to assess the risk of bias if RoB 2 has been incorporated into the software when this stage of the review is reached, otherwise we will use the Microsoft Excel RoB 2 tool (RoB 2 2019). We will provide the RoB 2 raw data file as an appendix in the published review.

The outcomes, measurement methods and time points to be assessed for risk of bias include the following.

- Pain, measured by self-report at the intermediate-term and long-term time points previously defined.
- Function, measured by self report or objective assessment at the intermediate-term and long-term time points previously defined.
- Satisfaction or HRQoL, measured by self-report at the intermediate-term and long-term time points previously defined.
- Adverse events leading to medical intervention or discontinuation from study.

Cluster-randomised and cross-over trials

For cluster-randomised and cross-over trials we will follow the guidance from Cochrane Methods (we have been advised that new guidance is being drafted, and will use this if it is published before we start this section).

For cluster-randomised trials our approach will be as follows.

1. Start with RoB 2.
2. Refer to Section 23.1.2 and Table 23.1 of the *Handbook* (Higgins 2019).
3. Add the additional domain 'Bias arising from the timing of identification and recruitment of participants', and use the signalling questions in Domain 1b in the archived version of the guidance document for cluster-randomised trials (Eldridge 2016).

For cross-over trials our approach will be as follows.

1. Start with RoB 2.
2. Refer to Section 23.2.3 and Table 23.2.a of the *Handbook* (Higgins 2019).
3. For Domain 2 'Bias due to deviations from intended interventions', use the signalling questions from Domain 2 in the archived version of the guidance document for cross-over trials (Higgins 2016).
4. For Domain 3 'Bias due to missing outcome data', answer question 3.2 in the standard RoB 2 using signalling question 3.2 in the archived version of the guidance document for cross-over trials (Higgins 2016).

Conflicts of interest and risk of bias

We will assess whether or not there is reason for 'notable concern' about conflicts of interest for each study. We will include a table

indicating our judgement for each study and provide a rationale for each assessment. We will define a notable concern as described in (Boutron 2019), "important conflicts of interest expected to have a potential impact on study design, risk of bias in study results or risk of bias in a synthesis due to missing results".

Assessment of bias in conducting the systematic review

We will conduct the review according to this published protocol and report any deviations from it in the 'Differences between protocol and review' section of the systematic review.

Measures of treatment effect

We will analyse dichotomous data as risk ratios (RR) and continuous data as mean difference, or standardised mean difference for results across studies with outcomes that are conceptually the same but measured on different scales. We will report corresponding 95% CIs. We will enter data presented as a scale with a consistent direction of effect.

Unit of analysis issues

A cluster-randomised trial may have participants with one neuroma in either foot or multiple neuromas in one foot. Studies included in meta-analyses may randomise at either the participant or neuroma level. Where cluster randomisation (that is, randomisation at the participant level) occurs, we will calculate effective sample sizes following the guidance in Section 23.1.4 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019). Different cluster randomisation scenarios include randomisation occurring at the participant level with individual outcome judgements recorded for multiple neuromas (e.g. all neuromas treated using the same intervention within a participant), or randomisation occurring at the neuroma level with individual outcome judgements recorded for multiple neuromas (i.e. within a participant neuromas may be treated with different interventions). We will calculate effective sample sizes where the number of Morton's neuromas and number of participants are known. If the intracluster correlation coefficient is not reported, we will conservatively assume it to be 0.05. When we include clustered studies in a meta-analysis, we will report the effective sample size per Morton's neuroma not per participant. We will conduct sensitivity analysis to investigate any change in effect size with the inclusion of cluster-randomised studies. When a cluster-randomised trial lacks the detail required to appropriately analyse the data (e.g. there is not enough information to conduct approximate analyses of cluster-randomised trials for a meta-analysis by calculating an effective sample size or inflating the standard error), we will present these studies in a table in the results and not include them in the meta-analysis.

In cross-over trials where randomisation occurs at the participant level (e.g. one neuroma in one foot), we will assess whether the first intervention will lead to a carry-over effect causing permanent or long-term modification of the condition. When this occurs, we will only use data from the first period, following the guidance in Section 23.2.4 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019). Where there is no carry-over effect from the first period, we will follow the guidance in Section 23.2.5 of the *Handbook* (Higgins 2019). Where randomisation occurs at the neuroma level (e.g. one neuroma in either foot) and separate interventions and outcome judgements are made for each foot/neuroma, we will follow the guidance in Section 23.2.5 of the *Handbook* (Higgins 2019). Our analysis will account for the pairing of feet/neuroma within individuals in the same way that pairing of intervention periods is recognised in the analysis of a cross-over trial. We will analyse the data as if it were achieved from the first period of a cross-over trial, and will follow the guidance in Section 23.2.4 of the *Handbook* (Higgins 2019). When a meta-analysis includes cross-over trials, we will follow the guidance in Sections 23.2.6 and 23.2.7 (Higgins 2019).

Where a single study reports more than two intervention groups, we will report all intervention groups in the table of 'Characteristics of included studies' but only include detailed descriptions of intervention groups relevant to the review topic. We will follow the guidance in Section 23.3.2 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019). We will only include these relevant groups in a meta-analysis. For studies with more than two relevant intervention groups (e.g. intervention A versus intervention B versus control), we will combine intervention A and intervention B for the analysis if they have a similar therapeutic target or mechanism. Where intervention A and intervention B have a different therapeutic target or mechanism, we will divide results from the control group evenly for separate comparisons against the two interventions. For both strategies, we will follow the guidance in Section 23.3.4 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019).

In the extremely unlikely event that there are one or more neuromas in one foot and multiple neuromas in the other foot, we may ask for additional statistical support from Cochrane Neuromuscular to guide our analysis and synthesis of these studies.

Dealing with missing data

We will contact investigators or study sponsors in order to verify key study characteristics and obtain missing numerical outcome data when necessary (e.g. when a study is available as an abstract only). Where possible, we will extract data to allow an intention-to-treat (ITT) analysis including all randomised participants according to the groups to which they were originally assigned. For missing summary data, we will calculate standard deviations from other statistics such as standard errors, CIs or P values, using the calculator function within RevMan Web 2021.

Assessment of heterogeneity

We will use the I^2 statistic to measure heterogeneity among the trials in each analysis. If substantial unexplained heterogeneity is identified in any of the analyses, we will report it and then explore possible causes for this heterogeneity by repeating the analyses after stratifying by study type. We will use the rough guide to interpretation as outlined in Section 10.10.2 of the *Handbook*, as follows.

- 0% to 40%: might not be important.
- 30% to 60%: may represent moderate heterogeneity.
- 50% to 90%: may represent substantial heterogeneity.
- 75% to 100%: considerable heterogeneity.

We will avoid the use of absolute cut-off values, but interpret I^2 in relation to the size and direction of effects and strength of evidence for heterogeneity (e.g. P value from the Chi^2 test, or CI for I^2) (Deeks 2019).

Assessment of reporting biases

If we are able to pool more than 10 trials, we will create and examine a funnel plot to explore possible publication bias. If searches identify trial protocols, clinical trial registrations or abstracts indicating the existence of unpublished studies, we will attempt to determine the status of any unpublished studies by contact with the investigators.

Data synthesis

We will group the data into similar interventions (e.g. similar therapeutic targets or mechanisms) and pool trial data by outcome if they measure the same construct (e.g. pain) and have scales that can be combined for analysis (e.g. both use continuous scales). To clarify the term 'similar intervention', we would combine the same drug class of corticosteroid injection data since they would have a similar therapeutic target. We would not combine corticosteroid injection and Botox injection data since they do not have a similar therapeutic target. Separate to data synthesis, we will group similar interventions together, such as corticosteroid injection and Botox injection (both being nonsurgical invasive interventions) for the grouping of intervention types in our results and summary of findings table.

Data synthesis methods

As a general rule, we will use the random-effects model in RevMan Web 2021, as this is usually a more conservative approach. Where the weightings given to individual studies comprising a meta-analysis are influenced by a small number of trials, we will perform a sensitivity analysis to determine whether their results are systematically different, since in these circumstances, use of a random-effects meta-analysis will exacerbate the effects of the bias. If they are systematically different, we will report both analyses. Where the studies are very homogeneous, such as similar design and same population, we will use a fixed-effect model.

Incorporating bias in data synthesis

We will incorporate risk of bias assessments in our analyses by presenting all studies and providing a narrative description of the risk of bias.

Narrative synthesis

If meta-analysis is not possible, we will provide a narrative synthesis of the available data following the guidance in Section 12.2.1 of the *Handbook* (McKenzie 2019).

Subgroup analysis and investigation of heterogeneity

We do not plan to perform any subgroup analyses.

Sensitivity analysis

We plan to perform the following sensitivity analyses.

- Repeat the analysis excluding studies with outcomes graded with an overall high risk of bias.
- Repeat the analysis excluding unpublished studies (if there are any).

Reaching conclusions

We will base our conclusions only on findings from the quantitative or narrative synthesis of included studies for this review. We will avoid making recommendations for practice; our implications for research will suggest priorities for future research and outline what the remaining uncertainties are in the area.

Summary of findings and assessment of the certainty of the evidence

We will create a summary of findings table using GRADEpro GDT software, and present the following outcomes.

Nonsurgical

- Pain: between-group difference in pain measured by self-report using a standardised questionnaire (e.g. VAS pain scale) assessed in the intermediate term (three months to less than 12 months from baseline).
- Function: change in function measured by self-report or objective measure of functional capacity using a standardised questionnaire (e.g. Foot Function Index disability or activity limitation subscales or six-minute walk test) assessed in the intermediate term (three months to less than 12 months from baseline).
- Satisfaction or HRQoL: level of satisfaction measured by self-report using a standardised questionnaire (e.g. Johnson scale) assessed in the intermediate term (three months to less than 12 months from baseline).
- Adverse events leading to medical intervention or discontinuation from study.

Surgical

- Pain: between-group difference in pain measured by self-report using a standardised questionnaire (e.g. VAS pain scale) assessed in the long term (12 months or longer from baseline).
- Function: change in function measured by self-report or objective measure of functional capacity using a standardised questionnaire (e.g. Foot Function Index disability or activity limitation subscales or six-minute walk test) assessed in the long term (12 months or longer from baseline).
- Satisfaction or HRQoL: level of satisfaction measured by self-report using a standardised questionnaire (e.g. Johnson scale) assessed in the long term (12 months or longer from baseline).
- Adverse events leading to medical intervention or discontinuation from study.

Two review authors (BM and MH) will use the five GRADE considerations (risk of bias, inconsistency of effect, imprecision, indirectness and publication bias) to independently assess the certainty of the body of evidence (studies that contribute data for the prespecified outcomes). We will use methods and recommendations described in Chapter 14 of the *Handbook* (Schünemann 2019). We will resolve any disagreements by discussion or by involving another author (CT). We will assess the certainty of the evidence according to the GRADE criteria. We will consider RCTs as providing high-certainty evidence if the five GRADE criteria above are not present to any serious degree, but may downgrade the certainty to moderate, low, or very low. We will downgrade evidence once if a GRADE consideration is serious and twice if very serious. We will justify all decisions to downgrade or upgrade the quality of studies using footnotes, and make comments to aid readers' understanding of the review where necessary.

ACKNOWLEDGEMENTS

The authors wish to thank the following people for providing their valuable input with the writing of this protocol:

Dr Ruth Brassington, Managing Editor, Cochrane Neuromuscular Disease Group, UK.

Prof. Joshua Burns, Editorial Board, Cochrane Neuromuscular Disease Group, Australia.

Dr Farhad Shokraneh, Information Specialist, Cochrane Neuromuscular Disease Group, UK. Updated the search strategy in consultation with the review authors.

Dr Kelly Gray, Faculty of Medicine, Health and Human Sciences, Macquarie University, Australia. Reviewer

Dr Fiona Hawke, School of Health Sciences, University of Newcastle, Australia. Reviewer

A/Prof. Cylie Williams, School of Primary and Allied Health Care, Monash University, Australia. Reviewer

Dr Janet Wale, Consumer Referee, Australia. Reviewer

Dr Sarah Nevitt, Department of Biostatistics, University of Liverpool, UK. Reviewer

Dr Kerry Dwan, Statistical Editor, Cochrane Editorial and Methods Department, UK. Reviewer

Ms Theresa Moore, Cochrane Editorial and Methods Department, UK. Reviewer

The Methods section of this protocol is based on a template developed by Cochrane Neuromuscular from an original created by Cochrane Airways.

This project was supported by the National Institute for Health Research (NIHR), via Cochrane Infrastructure funding to Cochrane Neuromuscular. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health. Cochrane Neuromuscular is also supported by the Queen Square Centre for Neuromuscular Disease.

REFERENCES

Additional references

Akermark 2008

Akermark C, Crone H, Saartok T, Zuber Z. Plantar versus dorsal incision in the treatment of primary intermetatarsal Morton's neuroma. *Foot and Ankle International* 2008;**29**(2):136-41. [DOI: 10.3113/FAI.2008.0136]

Aydinlar 2014

Aydinlar EI, Uzun M, Beksac B, Ozden VE, Karaarslan E, Oge AE. Simple electrodiagnostic method for Morton neuroma. *Muscle & Nerve* 2014;**49**(2):193-7. [DOI: 10.1002/mus.23899]

Barrett 2005

Barrett SL, Jarvis J. Equinus deformity as a factor in forefoot nerve entrapment: treatment with endoscopic gastrocnemius recession. *Journal of the American Podiatric Medical Association* 2005;**95**(5):464-8. [DOI: 10.7547/0950464]

Bennett 1995

Bennett GL, Graham CE, Mauldin DM. Morton's interdigital neuroma: a comprehensive treatment protocol. *Foot and Ankle International* 1995;**16**(12):760-3. [DOI: 10.1177/107110079501601204]

Betts 1940

Betts LO. Morton's metatarsalgia: neuritis of the fourth digital nerve. *Medical Journal of Australia* 1940;**1**(15):514-5. [DOI: 10.5694/j.1326-5377.1940.tb46191.x]

Bignotti 2015

Bignotti B, Signori A, Sormani MP, Molfetta L, Martinoli C, Tagliafico A. Ultrasound versus magnetic resonance imaging for Morton neuroma: systematic review and meta-analysis. *European Radiology* 2015;**25**(8):2254-62. [DOI: 10.1007/s00330-015-3633-3]

Bossley 1980

Bossley CJ, Cairney PC. The intermetatarsophalangeal bursa-its significance in Morton's metatarsalgia. *Journal of Bone and Joint Surgery* 1980;**62-B**(2):184-7. [PMID: 7364832]

Boutron 2019

Boutron I, Page MJ, Higgins JP, Altman DG, Lundh A, Hróbjartsson A, editor(s). Chapter 7: Considering bias and conflicts of interest among the included studies. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editor(s). Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019). Cochrane, 2019. Available from www.training.cochrane.org/handbook.

Bucknall 2016

Bucknall V, Rutherford D, MacDonald D, Shalaby H, McKinley J, Breusch SJ. Outcomes following excision of Morton's interdigital neuroma: a prospective study. *Bone and Joint Journal* 2016;**98-B**(10):1376-81. [DOI: 10.1302/0301-620X.98B10.37610]

Cashley 2015

Cashley DG, Cochrane L. Manipulation in the treatment of plantar digital neuralgia: a retrospective study of 38 cases. *Journal of Chiropractic Medicine* 2015;**14**(2):90-8. [DOI: 10.1016/j.jcm.2015.04.003]

Covidence [Computer program]

Veritas Health Innovation Covidence. Version accessed 12 April 2020. Melbourne, Australia: Veritas Health Innovation. Available at www.covidence.org.

Dando 2017

Dando C, Cherry L, Jones L, Bowen C. The clinical diagnosis of symptomatic forefoot neuroma in the general population: a Delphi consensus study. *Journal of Foot and Ankle Research* 2017;**10**(1):59. [DOI: 10.1186/s13047-017-0241-2]

Deeks 2019

Deeks JJ, Higgins JP, Altman DG, editor(s). Chapter 10: Analysing data and undertaking meta-analyses. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch, VA, et al editor(s). Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019). Cochrane, 2019. Available from www.training.cochrane.org/handbook.

de Oliveira 2019

de Oliveira HA, Natour J, Vassalli M, Rosenfeld A, Jennings F, Jones A. Effectiveness of customized insoles in patients with Morton's neuroma: a randomized, controlled, double-blind clinical trial. *Clinical Rehabilitation* 2019;**33**(12):1898-907. [DOI: 10.1177/0269215519873949]

Dockery 1999

Dockery GL. The treatment of intermetatarsal neuromas with 4% alcohol sclerosing injections. *Journal of Foot and Ankle Surgery* 1999;**38**(6):403-8. [DOI: 10.1016/s1067-2516(99)80040-4]

Durlacher 1845

Durlacher L. A treatise on corns, bunions, the disease of nails, and the general management of the feet. Simpkin, Marshall and Co, 1845.

Eldridge 2016

Eldridge S, Campbell M, Campbell M, Drahota A, Giraudeau, Higgins J, et al. Revised Cochrane risk of bias tool for randomized trials (RoB 2.0). Additional considerations for cluster-randomized trials. Available from: www.riskofbias.info/welcome/rob-2-0-tool/archive-rob-2-0-cluster-randomized-trials-2016.

Gallagher 2001

Gallagher EJ, Liebman M, Bijur PE. Prospective validation of clinically important changes in pain severity measured on a visual analog scale. *Annals of Emergency Medicine* 2001;**38**(6):633-8. [DOI: 10.1067/mem.2001.118863]

Gaynor 1989

Gaynor R, Hake D, Spinner SM, Tomczak RL. A comparative analysis of conservative versus surgical treatment of Morton's

neuroma. *Journal of the American Podiatric Medicine Association* 1989;**79**(1):27-30. [DOI: 10.7547/87507315-79-1-27]

Giakoumis 2013

Giakoumis M, Ryan JD, Jani J. Histologic evaluation of intermetatarsal Morton's neuroma. *Journal of the American Podiatric Medical Association* 2013;**103**(3):218-22. [DOI: 10.7547/1030218]

Govender 2007

Govender N, Kretzmann H, Price JL, Brantingham JW, Globe G. A single-blinded randomized placebo-controlled clinical trial of manipulation and mobilization in the treatment of Morton's neuroma. *Journal of the American Chiropractic Association* 2007;**44**(3):8-18. [3400152]

Govsa 2005

Govsa F, Bilge O, Ozer MA. Anatomical study of the communicating branches between the medial and lateral plantar nerves. *Surgical and Radiologic Anatomy* 2005;**27**(5):377-81. [DOI: 10.1007/s00276-005-0009-4]

GRADEpro GDT [Computer program]

McMaster University (developed by Evidence Prime) GRADEpro GDT. Version accessed 15 May 2020. Hamilton (ON): McMaster University (developed by Evidence Prime). Available at gradepro.org.

Higgins 2016

Higgins JP, on behalf of the RoB 20 working group on cross-over trials. Revised Cochrane risk of bias tool for randomized trials (RoB 2.0). Additional considerations for cross-over trials. Available from: www.riskofbias.info/welcome/rob-2-0-tool/archive-rob-2-0-cross-over-trials-2016.

Higgins 2019

Higgins JP, Eldridge S, Li T editor(s). Chapter 23: Including variants on randomized trials. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editor(s). Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019). Cochrane, 2019. Available from www.training.cochrane.org/handbook.

Hirschberg 2000

Hirschberg GG. A simple cure for Morton's neuralgia. *Journal of the American Podiatric Medical Association* 2000;**90**(2):100-1. [DOI: 10.7547/87507315-90-2-100]

Hughes 2007

Hughes RJ, Ali K, Jones H, Kendall S, Connell DA. Treatment of Morton's neuroma with alcohol injection under sonographic guidance: follow-up of 101 cases. *American Journal of Roentgenology* 2007;**188**(6):1535-9. [DOI: 10.2214/AJR.06.1463]

Jia 2017

Jia Y, Huang H, Gagnier JJ. A systematic review of measurement properties of patient-reported outcome measures for use in patients with foot or ankle diseases. *Quality of Life Research* 2017;**26**(8):1969-2010. [DOI: 10.1007/s11136-017-1542-4]

Johnson 1988

Johnson JE, Johnson KA, Unni KK. Persistent pain after excision of an interdigital neuroma. Results of reoperation. *The Journal of Bone and Joint Surgery* 1988;**70**(5):651-7.

Kilmartin 1994

Kilmartin TE, Wallace WA. Effect of pronation and supination orthosis on Morton's neuroma and lower extremity function. *Foot and Ankle International* 1994;**15**(5):256-62. [DOI: 10.1177/107110079401500505]

Larson 2005

Larson EE, Barrett SL, Battiston B, Maloney CT Jr, Dellon AL. Accurate nomenclature for forefoot nerve entrapment: a historical perspective. *Journal of the American Podiatric Medical Association* 2005;**95**(3):298-306. [DOI: 10.7547/0950298]

Latinovic 2006

Latinovic R, Guilliford MC, Hughes RA. Incidence of compressive neuropathies in primary care. *Journal of Neurology, Neurosurgery and Psychiatry* 2006;**77**:263-5. [DOI: 10.1136/jnnp.2005.066696]

Lee 2017

Lee J, Kim J, Lee M, Chu I, Lee S, Gwak H. Morton's neuroma (interdigital neuralgia) treated with metatarsal sliding osteotomy. *Indian Journal of Orthopaedics* 2017;**51**:692-6.

Levitsky 1993

Levitsky KA, Alman BA, Jevsevar DS, Morehead J. Digital nerves of the foot: anatomic variations and implications regarding the pathogenesis of interdigital neuroma. *Foot and Ankle* 1993;**14**(4):208-14. [DOI: 10.1177/107110079301400406]

Lizano-Diez 2017

Lizano-Díez X, Ginés-Cespedosa A, Alentorn-Geli E, Pérez-Prieto D, González-Lucena G, Gamba C, et al. Corticosteroid injection for the treatment of Morton's neuroma: a prospective, double-blinded, randomized, placebo-controlled trial. *Foot and Ankle International* 2017;**38**(9):944-51. [DOI: 10.1177/1071100717709956]

Mahadevan 2015

Mahadevan D, Venkatesan M, Bhatt R, Bhatia M. Diagnostic accuracy of clinical tests for Morton's neuroma compared with ultrasonography. *Journal of Foot and Ankle Surgery* 2015;**54**(4):549-53. [DOI: 10.1053/j.jfas.2014.09.021]

Mahadevan 2016

Mahadevan D, Attwal M, Bhatt R, Bhatia M. Corticosteroid injection for Morton's neuroma with or without ultrasound guidance: a randomised controlled trial. *Bone and Joint Journal* 2016;**98-B**(4):498-503. [DOI: 10.1302/0301-620X.98B4.36880]

Matthews 2019

Matthews BG, Hurn SE, Harding MP, Henry RA, Ware RS. The effectiveness of non-surgical interventions for common plantar digital compressive neuropathy (Morton's neuroma): a systematic review and meta-analysis. *Journal of Foot and Ankle Research* 2019;**12**(1):12. [DOI: 10.1186/s13047-019-0320-7]

McKenzie 2019

McKenzie JE, Brennan SE editor(s). Chapter 12: Synthesizing and presenting findings using other methods. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editor(s). Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019). Cochrane, 2019. Available from www.training.cochrane.org/handbook.

McQuay 1997

McQuay HJ, Moore RA, Eccleston C, Morley S, Williams AC. Systematic review of outpatient services for chronic pain control. *Health Technology Assessment* 1997;**1**(6):1-135. [PMID: 9483161]

Morton 1876

Morton TG. A peculiar and painful affection of the fourth metatarsophalangeal articulation. *American Journal of Medical Science* 1876;**71**(35):37-45.

Mulder 1951

Mulder JD. The causative mechanism in Morton's metatarsalgia. *Journal of Bone and Joint Surgery. British Volume* 1951;**33B**:94-5. [PMID: 14814167]

Naraghi 2016

Naraghi R, Bremner A, Slack-Smith L, Bryant A. The relationship between foot posture index, ankle equinus, body mass index and intermetatarsal neuroma. *Journal of Foot and Ankle Research* 2016;**9**:46. [DOI: 10.1186/s13047-016-0179-9]

NCBI 2021

US National Library of Medicine. National Library of Medicine Medical Subject Heading: Morton neuroma. www.ncbi.nlm.nih.gov/mesh/2016292 (accessed 24 May 2021).

Nissen 1948

Nissen KI. Plantar digital neuritis Morton's metatarsalgia. *Journal of Bone and Joint Surgery* 1948;**30**(1):84-94. [PMID: 18864949]

Nunan 1997

Nunan PJ, Giesy BD. Management of Morton's neuroma in athletes. *Clinics in Podiatric Medicine and Surgery* 1997;**14**(3):489-501. [PMID: 9257036]

Park 2017

Park YH, Jeong SM, Choi GW, Kim HJ. The role of the width of the forefoot in the development of Morton's neuroma. *Bone and Joint Journal* 2017;**99-B**(3):365-8. [DOI: 10.1302/0301-620X.99B3.BJJ-2016-0661.R1]

Park 2018

Park YH, Lee JW, Choi GW, Kim HJ. Risk factors and the associated cutoff values for failure of corticosteroid injection in treatment of Morton's neuroma. *International Orthopaedics* 2018;**42**(2):323-9. [DOI: 10.1007/s00264-017-3707-8]

Pasero 2006

Pasero G, Marson P. Filippo Civinini (1805-1844) and the discovery of plantar neuroma [Filippo Civinini (1805-1844) e la scoperta del neurinoma plantare]. *Reumatismo* 2006;**58**(4):319-22. [DOI: 10.4081/reumatismo.2006.319]

Pasquali 2015

Pasquali C, Vulcano E, Novario R, Varotto D, Montoli C, Volpe A. Ultrasound-guided alcohol injection for Morton's neuroma. *Foot and Ankle International* 2015;**36**(1):55-9. [DOI: 10.1177/1071100714551386]

RevMan Web 2021 [Computer program]

The Cochrane Collaboration Review Manager Web (RevMan Web). Version 3.0.0. The Cochrane Collaboration, 2021. Available at: revman.cochrane.org.

RoB 2 2019

Cochrane. Microsoft Excel 'Risk of bias 2' tool 2019. www.riskofbias.info (accessed 12 April 2020).

Samaila 2020

Samaila E, Colò G, Rava A, Negri S, Valentini R, Felli L, et al. Effectiveness of corticosteroid injections in Civinini-Morton's syndrome: a systematic review. *Foot and Ankle Surgery* 2020;**27**(4):357-65. [DOI: https://doi.org/10.1016/j.fas.2020.05.001]

Schünemann 2019

Schünemann HJ, Higgins JP, Vist GE, Glasziou P, Akl EA, Skoetz N, et al editor(s). Chapter 14: Completing 'Summary of findings' tables and grading the certainty of the evidence. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editor(s). Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019). Cochrane, 2019. Available from www.training.cochrane.org/handbook.

Seok 2016

Seok H, Kim SH, Lee SY, Park SW. Extracorporeal shockwave therapy in patients with Morton's neuroma: a randomized, placebo-controlled trial. *Journal of the American Podiatric Medical Association* 2016;**106**(2):93-9. [DOI: 10.7547/14-131]

Symeonidis 2012

Symeonidis PD, Iselin LD, Simmons N, Fowler S, Dracopoulos G, Stavrou P. Prevalence of interdigital nerve enlargements in an asymptomatic population. *Foot and Ankle International* 2012;**33**(7):543-7. [DOI: 10.3113/FAI.2012.0543]

Thomson 2013

Thomson CE, Beggs I, Martin DJ, McMillan D, Tudor Edwards R, Russell D, et al. Methylprednisolone injections for the treatment of Morton neuroma: a patient-blinded randomized trial. *Journal of Bone and Joint Surgery. American Volume* 2013;**95**(9):790-8, S1. [DOI: 10.2106/JBJS.I.01780] [3400160]

Van Hul 2011

Van Hul E, Vanhoenacker F, Van Dyck P, De Schepper A, Parizel PM. Pseudotumoural soft tissue lesions of the foot and ankle: a pictorial review. *Insights Imaging* 2011;**2**(4):439-52. [DOI: 10.1007/s13244-011-0087-2]

Villas 2008

Villas C, Florez B, Alfonso M. Neurectomy versus neurolysis for Morton's neuroma. *Foot and Ankle International* 2008;**29**(6):578-80. [DOI: 10.3113/FAI.2008.0578]

References to other published versions of this review

Thomson 2001

Thomson CE, Martin D, Gibson JNA. Interventions for the treatment of Morton's neuroma. *Cochrane Database of Systematic Reviews* 2001, Issue 2. Art. No: CD003118. [DOI: 10.1002/14651858.CD003118]

Thomson 2004

Thomson CE, Gibson JN, Martin D. Interventions for the treatment of Morton's neuroma. *Cochrane Database of Systematic Reviews* 2004, Issue 3. Art. No: CD003118. [DOI: 10.1002/14651858.CD003118.pub2]

APPENDICES

Appendix 1. NMD Specialised Register (CRS)

#1 MeSH DESCRIPTOR Neuroma AND INREGISTER

#2 neuroma* AND INREGISTER

#3 (#1 OR #2) AND INREGISTER

#4 (morton* OR foot OR feet) AND INREGISTER

#5 MeSH DESCRIPTOR Foot Diseases Explode All AND INREGISTER

#6 MeSH DESCRIPTOR Metatarsal Bones Explode All AND INREGISTER

#7 (#4 OR #5 OR #6) AND INREGISTER

#8 #3 AND #7 AND INREGISTER

#9 MeSH DESCRIPTOR Morton Neuroma Explode All AND INREGISTER

#10 (Morton NEAR Disease*) AND INREGISTER

#11 (morton NEAR metatarsalgia) AND INREGISTER

#12 (morton NEAR neuralgia) AND INREGISTER

#13 (intermetatarsal* NEAR neuroma*) AND INREGISTER

#14 (interdigital NEXT neuroma*) AND INREGISTER

#15 (#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14) AND INREGISTER

Abbreviations:

CRS: Cochrane Register of Studies; NMD: neuromuscular disease

Appendix 2. CENTRAL search strategy

#1 [mh ^Neuroma] or (neuroma*)

#2 (morton* or foot or feet)

#3 [mh "Foot Diseases"]

#4 [mh "Metatarsal Bones"]

#5 (#2 OR #3 OR #4)

#6 (#1 AND #5)

#7 [mh "Morton Neuroma"]

#8 Morton* NEAR Disease*

#9 morton NEAR/1 metatarsalgia

#10 morton NEAR neuralgia

#11 intermetatarsal* NEAR neuroma*

#12 interdigital NEXT neuroma*

#13 (#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12)

Appendix 3. MEDLINE (OvidSP) search strategy

Database: Ovid MEDLINE(R) <1946 to >
Search Strategy:
---

1 randomized controlled trial.pt.

2 controlled clinical trial.pt.

3 randomized.ab.

4 placebo.ab.

5 drug therapy.fs.

6 randomly.ab.

7 trial.ab.

8 groups.ab.

9 or/1-8

10 exp animals/ not humans.sh.

11 9 not 10

12 Neuroma/

13 neuroma$.mp.

14 12 or 13

15 (morton$ or foot$ or feet$).mp.

16 exp foot diseases/

17 metatarsal bones/

18 or/15-17

19 14 and 18

20 Morton Neuroma/

21 Morton$ Disease$.mp.

22 intermetatarsal$ adj1 neuroma$.mp.

23 interdigital neuroma$.mp.

24 Morton$ metatarsalgia$.mp.

25 morton$ neuralgia$.mp.

26 or/19-25

27 11 and 26

28 remove duplicates from 27

Appendix 4. Embase (OvidSP) search strategy

Database: Embase <1980 to >
Search Strategy:
---

1 Randomized Controlled Trial/

2 Clinical Trial/

3 Multicenter Study/

4 Controlled Study/

5 Crossover Procedure/

6 Double Blind Procedure/

7 Single Blind Procedure/

8 exp RANDOMIZATION/

9 Major Clinical Study/

10 PLACEBO/

11 Meta Analysis/

12 phase 2 clinical trial/ or phase 3 clinical trial/ or phase 4 clinical trial/

13 (clin$ adj25 trial$).tw.

14 ((singl$ or doubl$ or tripl$ or trebl$) adj25 (blind$ or mask$)).tw.

15 placebo$.tw.

16 random$.tw.

17 control$.tw.

18 (meta?analys$ or systematic review$).tw.

19 (cross?over or factorial or sham? or dummy).tw.

20 ABAB design$.tw.

21 or/1-20

22 human/

23 nonhuman/

24 22 or 23

25 21 not 24

26 21 and 22

27 25 or 26

28 Neuroma/

29 neuroma$.mp.

30 28 or 29

31 exp foot disease/

32 metatarsal bone/

33 (morton$ or foot$ or feet$).mp.

34 or/31-33

35 30 and 34

36 Morton Neuroma/

37 Morton$ Disease*.mp.

38 intermetatarsal$ adj1 neuroma$.mp.

39 interdigital neuroma$.mp.

40 Morton$ metatarsalgia$.mp.

41 morton$ neuralgia$.mp.

42 or/35-41

43 27 and 42

44 limit 43 to embase

45 remove duplicates from 44

Appendix 5. CINAHL Plus (EBSCOhost) search strategy

S29 S28 Limiters - Exclude MEDLINE Records

S28 S18 and S27

S27 S21 or S22 or S23 or S24 or S25 or S26

S26 Interdigital Neuroma*

S25 (MH "Morton's Neuroma")

S24 Morton* Neuralgia* OR (Morton* N1 Disease*)

S23 Morton* Metatarsalgia*

S22 Intermetatarsal* N1 Neuroma*

S21 S19 AND S20

S20 (MH "Foot Diseases+") or Morton* or Foot or Feet

S19 (MH "Neuroma") or Neuroma*

S18 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17

S17 ABAB Design*

S16 TI Random* or AB Random*

S15 (TI (Cross?Over or Placebo* or Control* or Factorial or Sham? or Dummy)) or (AB (Cross?Over or Placebo* or Control* or Factorial or Sham? or Dummy))

S14 (TI (Clin* or Intervention* or Compar* or Experiment* or Preventive or Therapeutic) or AB (Clin* or Intervention* or Compar* or Experiment* or Preventive or Therapeutic)) and (TI (Trial*) or AB (Trial*))

S13 (TI (Meta?Analys* or Systematic Review*)) or (AB (Meta?Analys* or Systematic Review*))

S12 (TI (Single* or Doubl* or Tripl* or Trebl*) or AB (Single* or Doubl* or Tripl* or Trebl*)) and (TI (Blind* or Mask*) or AB (Blind* or Mask*))

S11 PT ("Clinical Trial" or "Systematic Review")

S10 (MH "Factorial Design")

S9 (MH "Concurrent Prospective Studies") or (MH "Prospective Studies")

S8 (MH "Meta Analysis")

S7 (MH "Solomon Four-Group Design") or (MH "Static Group Comparison")

S6 (MH "Quasi-Experimental Studies")

S5 (MH "Placebos")

S4 (MH "Double-Blind Studies") or (MH "Triple-Blind Studies")

S3 (MH "Clinical Trials+")

S2 (MH "Crossover Design")

S1 (MH "Random Assignment") or (MH "Random Sample") or (MH "Simple Random Sample") or (MH "Stratified Random Sample") or (MH "Systematic Random Sample")

Appendix 6. ClinicalTrials.Gov

Advanced Search

Condition or disease: Morton Neuroma OR Morton's Neuroma OR Intermetatarsal Neuroma

Study type: Interventional Studies (Clinical Trials)

Appendix 7. WHO ICTRP

Advanced Search

Morton Neuroma OR Morton's Neuroma OR Intermetatarsal Neuroma in the Condition

Recruitment Status is ALL

CONTRIBUTIONS OF AUTHORS

BM:

- Designed the protocol
- Wrote the protocol
- Co-ordinated the protocol

CT:

- Conceived the protocol
- Designed the protocol
- Designed search strategy
- Wrote the protocol

JM:

- Assisted with writing the protocol

MH:

- Assisted with writing the protocol

RW:

- Assisted with writing the protocol

DECLARATIONS OF INTEREST

BM: none known; BM is a podiatrist and manages people with Morton's neuroma. He authored a 2019 systematic review of non-surgical interventions for Morton's neuroma.

CT: none known; CT is a surgical podiatrist and manages people with Morton's neuroma. He is an author of an RCT funded by the Chief Scientist Office Scottish Government, which is relevant to this systematic review.

JM: none known; JM is an orthopaedic surgeon who manages people with Morton's neuroma.

MH: none known; MH is a podiatrist and manages people with Morton's neuroma. He co-authored a 2019 systematic review of non-surgical interventions for Morton's neuroma.

RW: none known; RW is an academic biostatistician. He co-authored a 2019 systematic review of non-surgical interventions for Morton's neuroma.

SOURCES OF SUPPORT

Internal sources

- Queensland University of Technology, Australia

  BM: library access

External sources

- No sources of support provided